STANFORD CANCER INSTITUTE
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PHASE II STUDY OF EPACADOSTAT (INCB024360) WITH PEMBROLIZUMAB (MK-3475) IN METASTATIC OR UNRESECTABLE GASTROESOPHAGEAL JUNCTION AND GASTRIC ADENOCARCINOMA REQUIRING PAIRED BIOPSIES

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SUMMARY OF CHANGES

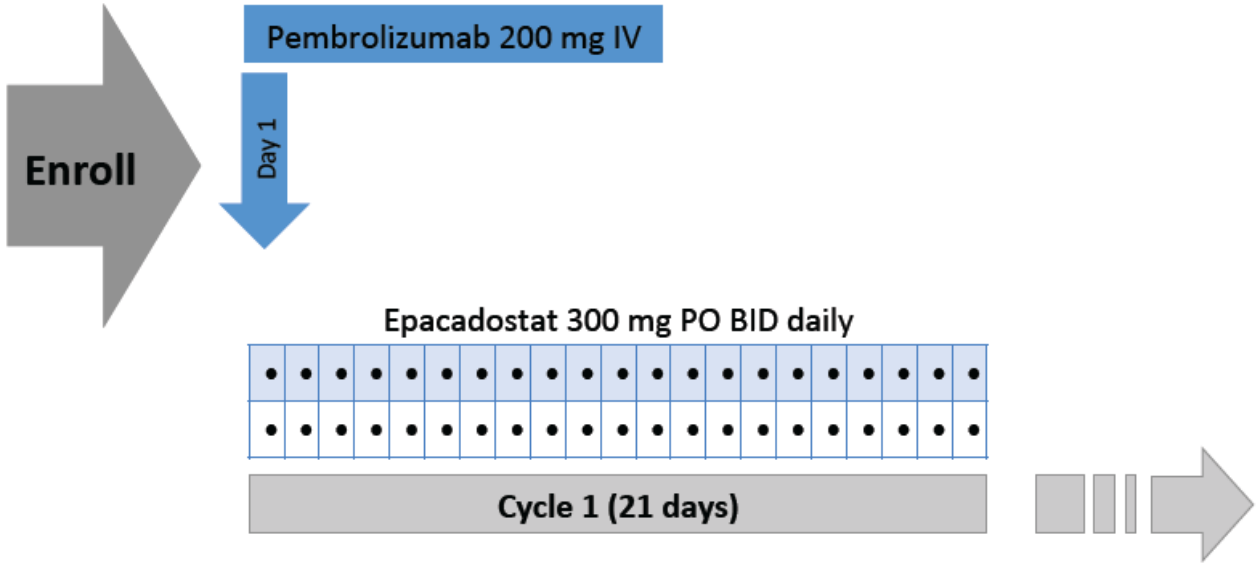
Compare v3.0 to v3.1

1. George A. Fisher, Jr., MD, PhD replaces Pamela Kunz, MD as Protocol Director and IND Sponsor.
    a. Cover page updated
    b. Section 7 updated with name of IND Sponsor
    c. Appendix A updated

PROTOCOL SYNOPSIS

TITLE	Phase II Study Of Epacadostat (INCB024360) With Pembrolizumab (MK-3475) In Metastatic Or Unresectable Gastroesophageal Junction And Gastric Adenocarcinoma Requiring Paired Biopsies
STUDY PHASE	II
INDICATION	Metastatic or unresectable gastroesophageal junction or gastric adenocarcinoma having progressed on at least one line of prior therapy for metastatic disease
INVESTIGATIONAL PRODUCTS	Epacadostat (INCB024360) Pembrolizumab (MK 3475)
PRIMARY OBJECTIVE(S)	To assess 6-month progression free survival (PFS)
SECONDARY OBJECTIVE(S)	To evaluate response rate (RR), overall survival (OS), and the safety and tolerability of Epacadostat (INCB024360) in combination with Pembrolizumab (MK3475) by CTCAE v5
TREATMENT SUMMARY	Non-randomized, single arm, open-label Oral Epacadostat at 300 mg twice daily + Intravenous Pembrolizumab at 200 mg every 3 weeks for up to 24 months
SAMPLE SIZE	30 patients undergoing pre- and on-treatment tumor biopsies
STATISTICAL CONSIDERATIONS	This is a single-stage study for the doublet epacadostat and pembrolizumab. A 6-month PFS of 20% was observed using single agent pembrolizumab and is the basis for the null hypothesis of the present study [1]. We will enroll 30 patients over 18 months and follow patients for at least 6 months. This design has 80% power to reject a 20% PFS rate, if the true PFS is 39%. Calculation based on binomial probabilities with a one-sided significance of 10%.

SCHEMA



Key Inclusion Criteria:

- Adenocarcinoma of the distal esophagus, gastroesophageal junction or stomach, including patients with HER2 + disease
- Patients must have metastatic or unresectable disease, including those with HER2+ disease having received Herceptin (trastuzumab)
- Must have progressed on at least one line of prior therapy for metastatic disease
- ECOG performance status 0 or 1
- Presence of measurable disease per RECIST v1.1, assessed within 4 weeks prior to study entry
- Tumor deemed amenable to biopsy by core or endoscopic biopsy
- Patient willing to undergo two newly-obtained biopsies - before and on-treatment, provided the procedure is not deemed high-risk and is clinically feasible

Primary Outcome: To assess 6-month progression free survival (PFS)

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA	Antidrug antibody
ADL	Activities of daily living
AE	Adverse event
AHSCT	Autologous hematopoietic stem cell transplant
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BID	Twice daily
BMI	Body mass index
BSA	Body surface area
CBC	Complete blood count
CFR	Code of Federal Regulations
CI	Confidence interval
CMAX	Maximum concentration of drug
CNS	Central nervous system
CR	Complete response
CRF	Case report/Record form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte-associated antigen-4
DC	Dendritic cell
DLCO	Diffuse lung capacity for carbon monoxide
DLT	Dose Limiting Toxicity
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EOT	End of treatment
ER	Estrogen receptor
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FIGO	International Federation of Gynecology and Obstetrics
FISH	Fluorescence in situ hybridization
GCP	Good Clinical Practice
GI	Gastrointestinal
GLP	Good Laboratory Practices
GU	Genitourinary
HBV	Hepatitis B virus
HCV	Hepatitis C virus

HER2	Human epidermal growth factor receptor 2
Hgb	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	Human Immunodeficiency Virus
HPF	High-power field
HPV	Human papillomavirus
HTN	Hypertensions
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDO1	Indoleamine 2,3 dioxygenase-1
IEC	Independent ethics committee
Ig	Immunoglobulin
IHC	Immunohistochemistry
IN	Investigator Notification
INR	International normalized ratio
irAE	Immune-related adverse event
IRB	Institutional Review Board
irRC	Immune-related response criteria
ITT	Intent to treat
IV	Intravenous
LFT	Liver function (chemistry) test
LH	Luteinizing hormone
LLN	Lower limit of normal
MAOI	Monoamine oxidase inhibitors
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NSAID	Nonsteroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PAD	Pharmacologically active dose
PD	Pharmacodynamic or progressive disease
PD-1	Programmed death receptor 1
PD-L1	Programmed death ligand 1
PET	Positron emission tomography
PFS	Progression free survival
PgR	Progesterone receptor
PK	Pharmacokinetic
PLT	Platelet
PR	Partial response
PT	Prothrombin time
RECIST v1.1	Response Evaluation Criteria In Solid Tumors Version 1.1
RP2D	Recommended Phase 2 dose

RR	Response rate
SAE	Serious adverse event
SD	Stable disease
SNRI	Serotonin/norepinephrine reuptake inhibitors
SS	Serotonin syndrome
SSRI	Serotonin reuptake inhibitors
SUSAR	Suspected unexpected serious adverse reaction
Treg	Regulatory T cell
TTP	Time to progression
ULN	Upper limit of normal
UNK	Unknown
WBC	White blood cell
WHO	World Health Organization

1. OBJECTIVES

1.1. Primary Objective

1.1.1. To assess 6-month progression free survival (PFS)

1.2. Secondary Objectives

1.2.1. To evaluate objective response rate (RR) by RECIST v1.1 and irRC

1.2.2. To evaluate overall survival (OS)

1.2.3. To assess the safety and tolerability of epacadostat in combination with pembrolizumab by NCI CTCAE v5

1.3. Exploratory Objectives

1.3.1. To determine the responder rate defined as the proportion of subjects with an increased ratio of CD8+ to Treg cells in on-treatment compared with pre-treatment biopsies

1.3.2. To identify putative immunologic biomarkers of tumor response

2. BACKGROUND

2.1. Study Disease

Gastroesophageal junction (GEJ) and gastric adenocarcinomas constitute a major health problem worldwide. Gastric cancer is the fourth most prevalent malignancy and the second leading cause of cancer death worldwide [2]. In the United States, an estimated 24,590 cases of gastric cancer will be diagnosed and 10,720 patients will die from this disease in 2015 [3]. Esophageal cancer is overall less common, but the incidence of adenocarcinoma of the esophagus, GEJ and gastric cardia has risen faster than any other malignancy in the last 25 years in the United States and other Western countries [4]. Although treatment for patients with unresectable or metastatic disease remains palliative, chemotherapy improves survival and quality of life when compared to best supportive care [5]. With standard treatment options, the progression free survival (PFS) for unresectable or metastatic disease is 4 to 6 months and median overall survival (OS) is 7 to 10

months. Recent trials in the second-line setting have shown median PFS is 2-3 months and median OS is 3-5 months [6, 7].

Data are emerging to suggest a role for checkpoint modulators in GEJ/gastric cancers and include antibodies against PD-L1 (atezolizumab)[8] and CTLA-4 (tremelimumab) [9]. Most recently, the KEYNOTE-012 study (NCT01848834), a multicenter, open-label, study of intravenous pembrolizumab included a cohort of 39 patients with PD-L1 expressing advanced gastric cancer. The majority of patients received ≥ 2 prior therapies. The 6-month PFS was 26%; median PFS was 1.9 months. 6-month OS was 66%, median OS was 11.4 months. 22% of patients achieved a partial response (PR) and 14% achieved stable disease as measured by RECIST v1.1 and central review.[1]

2.2. **Study Agent/Device/Procedure**

This is a Phase II study (IND #133705) of Epacadostat (INCB024360) administered in combination with pembrolizumab (Keytruda®, MK-3475). Epacadostat represents a novel, potent, and selective inhibitor of the enzyme indoleamine 2,3 dioxygenase-1 (IDO-1) in both human tumor cells and human dendritic cells (DCs). Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the immunoglobulin (Ig)G4/kappa isotype directed against programmed death receptor 1 (PD-1).

2.2.1. **Pharmaceutical and Therapeutic Background**

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades.[10] Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

2.2.2. **Inhibition of PD-1 as a Target for Cancer**

The PD-1 receptor-ligand interaction is a major pathway hijacked 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).[11, 12] The structure of murine PD-1 has been resolved. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade. 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.[13, 14] 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.[15, 16] Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and DCs.[17] 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, 18-20] Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. 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.[13] Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma.[21] 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.

Pembrolizumab, is a potent and highly selective humanized mAb of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda™ (Pembrolizumab) has recently been approved in the United Stated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

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

Recent interest has focused on the role of indoleamine 2,3–dioxygenase-1 (IDO-1) as a mechanism of induction of tolerance to malignancy.[22] IDO-1 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. IDO-1 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 IDO-1 are distinct from those of tryptophan dioxygenase, an enzyme predominantly expressed in liver that catalyzes the same enzymatic reaction as IDO-1 and maintains proper tryptophan balance in response to dietary uptake. In contrast to tryptophan dioxygenase, IDO-1 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.[23] Within the immune system, IDO-1 activity is specifically induced in cells such as DCs and macrophages at localized sites of inflammation.[24]

IDO-1 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.[25] Both the reduction in local tryptophan levels and the production of tryptophan catabolites that are inhibitory to cell proliferation contribute to the immunosuppressive effects.[26] IDO-1 activity also promotes the differentiation of naïve T-cells to cells with a regulatory phenotype (Treg).[27] 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[28]. IDO-1

expansion of Tregs may provide an additional mechanism whereby IDO-1 could promote an immunosuppressive environment.

The biological relevance of IDO-1 inhibition to immune tolerance was first demonstrated when it was shown that treating mice with a small molecule inhibitor of the IDO-1 pathway, 1-methyl-tryptophan, could break the tolerogenic state that protects allogeneic concept from the maternal immune system.[29] A critical role for IDO-1 in immunomodulation has been confirmed in numerous animal models, including models of allograft tolerance, inflammation, and cancer.[23] While IDO-1 inhibition can exacerbate disease in models of autoimmune disorders[23], IDO-1 null mice show no evidence of susceptibility to developing spontaneous autoimmunity or alterations in immune system development[25], suggesting that IDO-1 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 IDO-1 is a key regulator of the immunosuppressive mechanisms responsible for tumor escape from immune surveillance. Several groups have demonstrated that blockade of IDO-1 activity can directly influence the ability of tumor-bearing animals to reject tumors.[30, 31] In addition, studies with 1-methyl-tryptophan, demonstrate that IDO-1 inhibition dramatically increases the efficacy of various chemotherapeutic agents (e.g., platinum compounds, taxane derivatives, cyclophosphamide) without increased toxicity.[31] 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, IDO-1 appears to be chronically activated in subjects with cancer, and IDO-1 activation correlates with more extensive disease.[32, 33] IDO-1 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.[30, 34] Increased expression of IDO-1 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.[35-40]

Together, these results suggest that the IDO-1 pathway is a key regulatory element responsible for the induction and maintenance of tumor immune tolerance. Small molecule inhibitors of IDO-1 may provide an innovative and tractable method to treat advanced malignancies either alone or in combination with chemotherapeutics and/or immunotherapy-based strategies.

2.2.4. Combined Immune Checkpoint Inhibition

Blockade of immune inhibitory pathways is emerging as an important therapeutic modality for the treatment of cancer as evidenced by the clinical responses observed with antibodies to CTLA-4 and PD-1/PD-L1. Ipilimumab, a fully human, IgG1 mAb blocking CTLA-4, improved OS in patients with advanced melanoma.[41, 42] Nivolumab, a fully human IgG4 antibody blocking PD-1, produced durable objective responses in patients with melanoma, renal cell cancer, and non-small cell lung cancer (NSCLC).[43-45] 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.[46]

For example, CTLA-4 and PD-1 appear to play complementary roles in regulating adaptive immunity. Whereas PD-1 contributes to T-cell exhaustion in peripheral tissues, CTLA-4 inhibits at earlier points in T-cell activation. In preclinical models, combined blockade of PD-1 and CTLA-4 achieved more pronounced antitumor activity than blockade of either pathway alone.[47, 48]

On the basis of these observations, a Phase 1 study was conducted to investigate the safety and efficacy of combined CTLA-4 and PD-1 blockade (with the use of ipilimumab and nivolumab, respectively) in patients with advanced melanoma. The overall response rate (ORR) (according to modified World Health Organization criteria) for all patients in the concurrent-regimen group was 40%. Evidence of clinical activity (conventional, unconfirmed, or immune-related response or stable disease [SD] for ≥ 24 weeks) was observed in 65% of subjects. In 17 subjects treated at the maximum doses that were associated with an acceptable level of adverse events (AE), 53% of subjects had an objective response compared with ipilimumab monotherapy (10.9%), all with tumor reduction of ≥ 80%. Grade 3 or 4 AEs related to therapy occurred in 53% of subjects in the concurrent-regimen group but were qualitatively similar to previous experience with

monotherapy and were generally reversible. Among subjects in the sequenced-regimen group, 18% had Grade 3 or 4 AEs related to therapy and the ORR was 20%. Grade 3 or 4 AEs, regardless of attribution, were observed in 72% of subjects, and Grade 3 or 4 treatment-related AEs were noted in 53%. Serious adverse events (SAE) related to treatment were reported in 49% of patients in the concurrent regimen group. Common Grade 3 or 4 selected AEs that were related to the therapy included hepatic events (15%), gastrointestinal events (9%), and renal events (6%). Isolated cases of pneumonitis and uveitis were observed. In both regimen groups, treatment-related AEs were manageable and generally reversible with the use of immunosuppressants (or hormone-replacement therapy for endocrinopathies) according to previously established algorithms.[49]

As described above, IDO-1 is another negative regulatory mechanism that contributes to tumor-derived immune suppression. In preclinical models, IDO-1 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.[50, 51] 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.

The IDO-1 inhibitor epacadostat has completed a Phase 1 study and has several ongoing Phase 1 and Phase 2 studies in combination with immune-targeted agents, such as anti–PD-1, anti–PD-L1, and anti–CTLA-4 antibodies. In an ongoing study combining epacadostat and ipilimumab (INCB 24360-201) subjects received ipilimumab (3 mg/kg IV every 3 weeks x 4) with epacadostat at doses of 25 mg BID, 50 mg BID continuous, 50 mg BID intermittent (2 weeks on, 1 week off), and 75 mg (50 mg morning/25 mg night). A total of 42 subjects were enrolled: 25 mg BID (n=8), 50 mg BID (continuous) (n=18), 50 mg BID (intermittent) (n=9), and 75 mg (n=7). DLTs were: 25 mg BID, Grade 3 increased AST (n=1); 50 mg BID (continuous), Grade 3 diarrhea (n=1), Grade 3 increased ALT/AST (n=2), Grade 3 colitis (n=1), and Grade 3 pneumonitis (n=1); 50 mg BID (intermittent), Grade 3 colitis (n=1); 75 mg, Grade 3 rash (n=1). The most common all grade irAEs were rash (52.4%), pruritus (16%), diarrhea (33.3%), increased ALT (21.4%), increased AST (16.7%), and hypothyroidism (11.9%). Grade ≥3 irAEs occurred in 40% of subjects. The most common Grade ≥ 3 irAEs were increased AST (9.5%), increased ALT (7.1%), and colitis (9.5%). Among 32 immunotherapy-naïve subjects,

ORR was 31.3% (10/32) per irRC and 28.1% (9/32) per RECIST v1.1; complete response (CR) rate per both criteria was 9.4%. At data cutoff (August 2015), responses were ongoing in 6 subjects. The disease control rate (DCR) (CR + partial response [PR] + stable disease [SD]) was 62.5% (20/32) per irRC and 53.1% (17/32) per RECIST v1.1. Median progression free survival (PFS) was 8.2 months by irRC and 5.3 months by RECIST v1.1. Among 10 subjects previously treated with immunotherapy, the DCR by both criteria was 30% by irRC and RECIST v1.1 (all SDs).

In a recent Phase 1 study (INC 24360-202), safety, efficacy, and tolerability of the combination of pembrolizumab at a dose of 2 mg/kg IV every 3 weeks in combination with epacadostat at doses of 25 mg BID, 50 mg BID, 100 mg BID, and 300 mg BID and epacadostat 300 mg BID in combination with fixed dose of pembrolizumab 200 mg IV every 3 weeks in subjects with various solid tumors have been evaluated. A total of 61 subjects were enrolled as of October 2015. Preliminary safety data (unaudited) was evaluated for 56 out of 61 subjects: 25 mg BID (n=4), 50 mg BID (n=19), 100 mg BID (n=18), and 300 mg (n=15). The most common AEs (≥15%) any grade were rash, fatigue, nausea, cough, diarrhea, pyrexia, arthralgia, back pain, dyspnea and constipation; the majority of these were grade 1 or 2. Grade ≥3 irAEs were rash (n=3), AST increased (n=1) and bilirubin increased (n=1). Additional Grade ≥3 treatment-related AEs were mucosal inflammation, and neurologic event not otherwise specified (NOS) (n=1 each). The neurological event NOS, ataxia, was observed in a single subject, who had a history of brain metastases and prior radiotherapy, due to recurrent brain metastases.

AEs were, in general, well-tolerated. The events of rashes observed at the 300 mg BID cohort were reversible with dose interruptions and medical treatment. The total dose interruptions were higher in the 300 mg BID group with 6/15 interrupting epacadostat due to AEs compared to 1 subject in 100 mg BID, 2 subjects in 50 mg BID and 1 subject in 25 mg BID.

The safety profile for the 300mg bid dose of epacadostat in combination with pembrolizumab in the Phase I/II study (INCB24360-202) did not exceed the MTD in that study. While there was a higher incidence of grade 3 rash in the 300mg bid cohort compared to the 100mg bid cohort, these did not qualify as protocol-specified DLTs.

The dose combination of 100mg bid epacadostat plus pembrolizumab for the Phase III melanoma study (INCB24360-301) is based upon a benefit/risk assessment made specifically in

melanoma in collaboration with Merck. In the INCB24360-202 study, there was evidence of improved efficacy in melanoma subjects at all doses of epacadostat of from 50 to 300mg bid. Given that melanoma is an immunotherapy responsive tumor, and lower doses of epacadostat appeared to have similar activity, the decision was made to take the 100mg bid dose combination forward because of the lower incidence of dose interruptions and dose reductions compared to the 300mg bid dose.

However, in other tumor types, which appear to demonstrate more resistance to known immunotherapies, we believe that greater target coverage for inhibition of IDO1 may be necessary. The PK/PD modelling suggests that doses of 100mg bid epacadostat achieve an average IC50 at trough in most patients. At 300mg bid, epacadostat achieves target inhibition above the IC90 at trough. Greater target inhibition may be necessary in more resistant tumors, and potentially balances benefit/risk in favor of the higher epacadostat dose combination given that the dose does not exceed the MTD.

We now have a larger dataset with respect to the 300 mg bid dose in combination with anti-PD-1 and anti-PD-L1 antibodies. 300 mg is tolerated, and we have seen an increase in the incidence of grade 3 rash. However, these have been manageable with dose interruptions and occasionally with steroids. Our current thinking is to maximize the dose of epacadostat at 300mg bid in non-melanoma tumor types in order to achieve optimal target coverage.

In summary, both IDO-1 and PD-1 have been shown to suppress T-cell mediated antitumor immunity, and IDO-1 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.

2.3. **Rationale**

The goal of cancer immunotherapy is to initiate or reinitiate a self-sustaining cycle of cancer immunity, enabling it to amplify and propagate. Cancer immunotherapies must overcome the negative feedback mechanisms inherent in most cancers. The current approach will attempt to further amplify an immune response by targeting multiple nonredundant immune checkpoints. Expression of IDO-1 represents an early checkpoint that results in a diminished immune

response and tolerance to tumor antigen. Data are emerging to suggest a role for checkpoint modulators in GEJ/gastric cancers and we propose a single-institution, phase II, single-arm, non-randomized study investigating epacadostat and pembrolizumab in advanced GEJ and gastric adenocarcinoma.

An open-label Phase I trial (Protocol 001) is being conducted to evaluate the safety and clinical activity of single agent pembrolizumab. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg every 2 weeks). No maximum tolerated dose (MTD) has been identified to date. Recent data from other clinical studies within the pembrolizumab program has shown that a lower dose of pembrolizumab and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of pembrolizumab administered every 2 weeks and every 3 weeks showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic (PD) data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early pharmacokinetic (PK) and PD data provides scientific rationale for testing an every 2 week and every 3 week dosing schedule.

A population PK analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of pembrolizumab were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. Pembrolizumab has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg every 3 week body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for pembrolizumab in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg every 3 weeks vs. the proposed dose regimen of 2 mg/kg every 3 weeks (i.e., 5-fold higher dose

and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

The rationale for further exploration of 2 mg/kg and comparable doses of pembrolizumab in solid tumors is based on: 1) similar efficacy and safety of pembrolizumab when dosed at either 2 mg/kg or 10 mg/kg every 3 weeks in melanoma patients, 2) the flat exposure-response relationships of pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg every 3 weeks to 10 mg/kg every 3 weeks, 3) the lack of effect of tumor burden or indication on distribution behavior of pembrolizumab (as assessed by the population PK model) and 4) the assumption that the dynamics of pembrolizumab target engagement will not vary meaningfully with tumor type.

The choice of the 200 mg every 3 weeks as an appropriate dose for the switch to fixed dosing is based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response, and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe.

A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage.

2.3.1. Rationale for Studying Immunotherapy in Advanced or Metastatic Cancers

Cancer immunotherapies have recently have been approved by the United States Food and Drug Administration (FDA) in several tumor indications to date, such as melanoma and NSCLC. The efficacy of pembrolizumab was investigated in a multicenter, open-label, randomized (1:1), dose study in subjects with unresectable or metastatic melanoma with progression of disease; refractory to 2 or more doses of ipilimumab (3 mg/kg or higher) and, if BRAF V600 mutation-

positive, a BRAF or MEK inhibitor; and disease progression within 24 weeks following the last dose of ipilimumab. There were 173 subjects enrolled and the ORR was 24%, with 8 subjects with ongoing responses of 6 months or longer. There were also objective responses in subjects with and without BRAF V600 mutation-positive melanoma (Pembrolizumab package insert, 6/2015). Similarly, nivolumab demonstrated activity when given alone in subjects with progression of disease on or following ipilimumab treatment and, if BRAF V600 mutation-positive, a BRAF inhibitor. The study enrolled 120 subjects and the ORR was 32%, with 13 subjects with ongoing responses of 6 months or longer. There were also objective responses in subjects with and without BRAF V600 mutation-positive melanoma (Nivolumab package insert, 3/2105). More recently, nivolumab was tested in previously untreated melanoma without BRAF mutation, which similarly showed good response rates and improvement in OS when compared to dacarbazine. At 1 year, the overall rate of survival was 72.9% (95% confidence interval [CI], 65.5 to 78.9) in the nivolumab group, as compared with 42.1% (95% CI, 33.0 to 50.9) in the dacarbazine group (hazard ratio for death, 0.42; 99.79% CI, 0.25 to 0.73; $p < 0.001$). The ORR was 40.0% (95% CI, 33.3 to 47.0) in the nivolumab group versus 13.9% (95% CI, 9.5 to 19.4) in the dacarbazine group (odds ratio, 4.06; $p < 0.001$).[53] Nivolumab was also recently approved as a single agent for the treatment of subjects with metastatic squamous NSCLC with progression on or after platinum-based chemotherapy based on demonstration of superior overall survival versus docetaxel, with 41% reduction in risk of death in a prespecified interim analysis of a Phase 3 clinical study. The median OS was 9.2 months in the nivolumab group and 6 months in the docetaxel group.

First-line data in advanced or metastatic melanoma with pembrolizumab versus ipilimumab was recently presently at the annual meeting of the American Association for Cancer Research (AACR), with an estimated 46.4% 6-month PFS rate for pembrolizumab 2 mg/kg every 3 weeks versus 26.5% for ipilimumab. The ORR was 32.9% for pembrolizumab 2 mg/kg every 3 weeks versus 11.9% for ipilimumab. Responses were ongoing in 96.7% of subjects after a median follow-up of 7.9 months.[54] Median PFS was 4.1 months for pembrolizumab versus 2.8 months for ipilimumab. The hazard ratio for the disease progression for pembrolizumab every 3 weeks versus ipilimumab was 0.58 (95% CI, 0.47 to 0.72; $p < 0.001$). At the time of the data cutoff for the second interim analysis in this study, which was driven by a minimum follow-up

duration of 12 months for all subjects, 289 deaths occurred. One-year estimates of survival for subjects receiving pembrolizumab every 3 weeks was 68.4% as compared with ipilimumab 58.2% (hazard ratio for death as compared with ipilimumab group 0.69; 95% CI, 0.52 to 0.90; p = 0.0036). Because the OS results were superior to those for the ipilimumab group, the independent Data Monitoring Committee (DMC) recommended stopping the study early to allow subjects in the ipilimumab group the option of receiving pembrolizumab.[54]

In 38 subjects with previously treated advanced NSCLC treated with pembrolizumab at a dose of 10 mg/kg every 3 weeks, an ORR of 24% as measured by the irRC was observed,[45] with similar results using RECIST v1.1 (21%). Most responses were observed by the first planned assessment at week 9. Median duration of response by irRC has not been reached with a median duration of follow-up of 62 weeks. The median OS for all 38 subjects treated with pembrolizumab was 51 weeks.

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

A training set comprising approximately 140 tumor samples and their associated clinical outcome data were used to assess an optimal cut point for PD-L1 positivity. An optimal PD-L1 cut point was identified by receiver operator characteristic curve analyses and by considering clinical implications of false-positive and false-negative results. Cut points were identified based on a proportions score method of IHC analysis, with the tumors expressing at or greater than the

highest cut point (proportions score ≥ 50%) referred to as PD-L1 strong tumors, and tumors expressing > 1% but < 50% referred to as the PD-L1 weak tumors. Outcomes based in irRC were used as the primary outcome for the analysis. Based on the training set, the positive predictive value for subjects in the strong category was 42%, while maintaining a negative predictive value of 92% for subjects in the weak or null category.[55] This study completed, and a total of 495 subjects received pembrolizumab either 2 mg/kg every 2 weeks or 10 mg/kg every 3 weeks or 10 mg/kg every 2 weeks, and 182 subjects were assigned to the training group or a validation group (313 subjects). Among all subjects, the ORR was 19.4%, and the median duration of response was 12.5 months. The median duration of PFS was 3.7 months, and the median duration of OS was 12.0 months. PD-L1 expression in at least 50% of tumor cells was selected as the cutoff from the training group. Among subjects with a proportion score of at least 50% in the validation group, the response rate was 45.2%. Among all subjects with a proportion score of at least 50%, median PFS was 6.3 months; median OS was not reached. In summary, pembrolizumab had an acceptable side-effect profile and showed antitumor activity in subjects with advanced NSCLC. PD-L1 expression in at least 50% of tumor cells correlated with improved efficacy of pembrolizumab.[56]

Data are emerging to suggest a role for checkpoint modulators in GEJ/gastric cancers and include antibodies against PD-L1 (atezolizumab)[8] and CTLA-4 (tremelimumab).[9] In an open-label, Phase 1b study, the safety, tolerability, and antitumor activity of pembrolizumab were assessed in subjects with advanced solid tumors in the KEYNOTE-012 study (Clinicaltrials.gov: NCT01848834). In this study a cohort of 39 patients with PD-L1 expressing advanced gastric cancer, 22% of patients achieved a partial response (PR) and 14% achieved stable disease as measured by RECIST v1.1 and central review.[57]

Targeting PD-1 assumes that the T-cells are essentially exhausted (and thus tolerant of the tumor) and that this exhaustion may be reversed by blocking PD-1 signaling. Targeting IDO-1 will concurrently decrease infiltration of regulatory CD4+ cells and immune-suppressive cytokines. This novel combination strategy has strong biologic rationale and may augment and deepen response rates over and above that demonstrated with single agent PD-1 blockade. Thus, there is a strong rationale for therapies aimed at restoring antitumor immunocompetence and establishing a rationale for inhibiting IDO-1 and the PD-1/PD-L1 pathways.

In summary, both IDO-1 and PD-1 have been shown to suppress T-cell mediated antitumor immunity, and IDO-1 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.

2.4. **Study Design**

This is a single institution, non-randomized, single arm, open-label study for the doublet epacadostat and pembrolizumab. The primary purpose of this protocol is treatment, designed to evaluate one or more interventions for treating a disease, syndrome or condition.

2.5. **Correlative Studies Background and Rationale**

Blood and tissue will be collected for future correlative studies and stored at Stanford. For further information, see Section 9.0

- Blood: Plasma, and PBMC will be collected every three weeks for correlative studies.
- Tissue: Pre and on-treatment (day 42 ± 5 days) tissue biopsies will be collected for correlative studies.

3. PARTICIPANT SELECTION AND ENROLLMENT PROCEDURES

For entry into the study, the following criteria must be met. Please refer to Appendix A for the eligibility and verification checklist to assist with patient enrollment.

3.1. **Subject Population**

Subjects with metastatic or recurrent distal esophageal (within 5 cm of the GEJ), GEJ, or gastric adenocarcinoma who have had disease progression on at least one prior therapy or be intolerant to that therapy if they have not progressed. If the patient is HER2 + they must have received Herceptin (trastuzumab). At Stanford Cancer Institute (SCI) there will be 30 patients enrolled over the recruitment period.

3.2. **Inclusion Criteria**

In order to be eligible for participation in this study, the subject must meet all of the following:

3.2.1. Age ≥ 18 years of age on day of signing informed consent.

3.2.2. Be willing and able to provide written informed consent/assent for the study

3.2.3. Histologically or cytologically confirmed adenocarcinoma of the distal esophagus, gastroesophageal junction or stomach, including patients with HER2+ disease. Distal esophagus is defined as within 5 centimeters of the GEJ.

3.2.4. Patients must have metastatic or unresectable disease, including those with HER2+ disease.

3.2.5. Must have progressed on at least one line of prior therapy for metastatic disease, or be intolerant to that therapy if they have not progressed, and for HER2+ disease should have received prior trastuzumab.

3.2.6. Life expectancy ≥ 12 weeks

3.2.7. Have a performance status of 0 or 1 on the ECOG Performance Scale.

3.2.8. Have measurable disease per RECIST v1.1, assessed within 4 weeks prior to study entry.

3.2.9. Tumor deemed amenable to biopsy by core for metastatic site or endoscopic biopsy for primary tumor (for both before and on-treatment biopsies).

3.2.10. Patient must be willing to undergo two biopsies - before and on-treatment, provided the procedure is not deemed high-risk and is clinically feasible.

3.2.11. Demonstrate adequate organ function as defined in **Table 1**, all screening labs should be performed within 7 days of treatment initiation.

Table 1: Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L without transfusion or EPO dependency (within 7 days of assessment)
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine	≤1.5 X upper limit of normal (ULN) **OR**

clearance (GFR can also be used in place of creatinine or CrCl)	≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Total bilirubin	≤ 1.5 X ULN **OR** Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
Albumin	≥2.5 mg/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

3.2.12. Female subject of childbearing potential should have a negative urine or serum pregnancy within 3 days 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.

3.2.13. Female subjects of childbearing potential must be willing to use an adequate method of contraception starting with the date of consent through 120 days after the last dose of study medication. *Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.*

3.2.14. Male subjects of childbearing potential must agree to use an adequate method of contraception starting with the date of consent through 120 days after the last dose of study therapy. *Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.*

3.2.15. Must be able to swallow pills.

3.3. **Exclusion Criteria**

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

3.3.1. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first planned dose of treatment.

3.3.2. Has known hypersensitivity to pembrolizumab and/or Epacadostat or any of their excipients.

3.3.3. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or to baseline) from adverse events due to agents administered more than 4 weeks earlier. Note that denosumab for treatment for bone metastases is allowed.

3.3.4. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study day 1 or who has not recovered (i.e., ≤ Grade 1 or to baseline) from adverse events due to a previously administered agent.

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

- *Note:* If subject received major surgery, they must have recovered adequately from surgery prior to starting therapy.

3.3.5. Have been treated on any Merck-sponsored pembrolizumab-containing gastric cancer pivotal trial will require prior authorization by Merck in order to enroll in this study.

3.3.6. Has had prior therapy with IDO-inhibitors

3.3.7. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

3.3.8. Has known history of, or any evidence of active, non-infectious pneumonitis

3.3.9. Has received a live vaccine within 30 days of planned start of study therapy.

Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however, intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

3.3.10. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of study treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to study treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability. Patient with prior CNS metastases treated w/ prior RT will also need all of the following: A. 2 months off RT before starting study or 4 weeks following XRT if MRI is stable and the patient is off steroids, B. Baseline MRI with no edema, and C. stable for at least 8 weeks.

3.3.11. Has known additional malignancy that has progressed or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell

carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.

3.3.12. Has active infection requiring systemic therapy

3.3.13. Has a known history of active TB (Bacillus Tuberculosis)

3.3.14. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] detected)

3.3.15. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study medication

3.3.16. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies)

3.3.17. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study, starting with pre-screening or screening visit through 120 days after the last dose of study treatment

3.3.18. Has had monoamine oxidase inhibitors within 21 days before screening

3.3.19. Has any history of serotonin syndrome after receiving 1 or more serotonergic drugs

3.3.20. Has presence of a gastrointestinal condition that may affect drug absorption

3.3.21. Use of systemic corticosteroids

3.3.22. Has history or presence of an abnormal electrocardiogram (ECG) which, in the investigator's opinion, is clinically significant.

- QTcF > 480 ms or presence of a Left Bundle Branch Block (LBBB). If the QRS duration > 120ms, the JTc can be used in place of the QTcF. The JTc must be < 340 ms.

3.3.23. Has history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

3.3.24. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study.

3.3.25. Has known allergy or reaction to any component of either study drug or formulation components.

3.4. Informed Consent Process

All participants must be provided a consent form describing the study with sufficient information for participants to make an informed decision regarding their participation. Participants must sign the IRB approved informed consent prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

The granting of informed consent must be documented in writing, using an ICF that contains all the elements required by ICH E6 and describes the nature, scope, and possible consequences of the study in a form understandable to the study subject.

Subjects of childbearing potential must agree to take appropriate measures to avoid pregnancy in order to participate in the study.

3.5. Randomization Procedures

This is an open-label single-arm study, therefore, the investigator and subject will know the treatment administered and there is no randomization.

3.6. Study Timeline

3.6.1. Primary Completion

The study is expected to reach its accrual goal within 18 months from the time enrollment begins. Patients are anticipated to stay on treatment for 6 months. Thus, primary completion will take approximating 6 months from date of last patient enrolled. Upon completion of the last patient's last treatment, all patients will remain in long-term follow-up for evaluation of survival.

3.6.2. Study Completion

Patients will be followed for progression and survival. Estimated study completion is approximately 4 years from when study opens.

4. TREATMENT PLAN

4.1. Study Procedures

The schedule of events calendar (Section 9) summarizes the study procedures to be performed at

each visit. Individual study procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator. Furthermore, additional evaluations/testing may be deemed necessary by the investigator and/or Merck and Incyte 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.

4.2. **Duration of Treatment and Subject Participation**

Each subject enrolled in the study will continue receiving combination study treatment in continuous 21-day cycles for up to 24 months, and then treatment with monotherapy epacadostat may continue as long as the subject is receiving benefit from treatment and has not had disease progression or met any criteria for study withdrawal. If the subject discontinues all study treatment, the treatment phase will end, and the subject will enter the follow-up phase. Study participation is expected to average about 6 months.

4.3. **Screening Phase**

4.3.1. **Informed Consent**

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

4.3.2. **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 study.

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 study. 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 authorized representative's dated signature.

Specifics about a study and the study 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.

4.3.3. 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 study prior to starting them on the study.

Results from the screening visit evaluations will be reviewed to confirm subject eligibility before enrollment or the administration of study drug. Tests with results that fail eligibility requirements may be repeated once during the screening phase if the investigator believes the results to be in error. Additionally, a subject who fails screening may repeat the screening process 1 time if the investigator believes there has been a change in eligibility status (e.g., after recovery from an infection).

4.3.4. Demographics and Medical History

Demographic data and a complete medical and medication history will be collected at screening by the investigator or qualified designee and will include date of birth, race, ethnicity, medical and surgical history, and concurrent illnesses assessed using the NCI CTCAE v5. Medical history should include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the investigator. Details regarding the disease for which the subject has enrolled in this study (e.g., date of diagnosis, primary tumor histology, prior systemic therapies, surgeries, radiation therapy, and stage of cancer) will be recorded separately and not listed in medical history.

4.3.5. 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 28 days before starting the study. Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.

4.3.6. Concomitant Medications

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

All clinical, efficacy and laboratory procedures and assessments that will be administered at screening phase and treatment cycles are listed below.

4.3.7. Disease Details and Treatments

4.3.7.1. Disease Details

The investigator or qualified designee will obtain prior and current details regarding disease status.

4.3.7.2. Prior Treatment Details

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation therapy, and surgeries.

4.3.7.3. Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of study treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of study treatment, the 30-day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated, the subject will move into survival follow-up.

4.4. Treatment Phase

The treatment period with the combination therapy will continue every 21 days for up to 24 months. Single agent epacadostat may continue indefinitely beyond 24 months provided the patient has benefit.

4.4.1. Administration of Investigational Products

Study treatment should be administered on day 1 of each cycle (21 day cycles) after all procedures/assessments have been completed as detailed in the schedule of events calendar. Study treatment may be administered up to 3 days before or after the originally scheduled day 1 of each cycle due to administrative reasons. All study treatments will be administered on an outpatient basis.

4.4.2. Treatment Compliance

Treatment compliance with all study-related medications should be emphasized to the subject by the site personnel, and appropriate steps should be taken to optimize compliance during the study. Subjects will bring all bottles of unopened, empty, and unused epacadostat drug with them to each study visit. Investigative site staff will perform a count of returned tablets to assess compliance, and this information will be entered into the electronic case report form (eCRF).

4.4.2.1. Epacadostat (INCB024360)

Site staff will dispense medication sufficient for a 3-week cycle (21 days). Subjects will be administered study drug at 300 mg oral, twice daily, continuous dosing. All twice daily doses of epacadostat will be taken orally in the morning and evening, approximately 12 hours apart without regard to food. If the morning or evening dose is missed by more than 4 hours, that dose should be skipped and the next scheduled dose should be taken at the usual scheduled time. Doses of epacadostat will be self-administered except on the day of the cycle that the patient is visiting the study clinic for infusion (Day 1 of each cycle); epacadostat will be taken prior to pembrolizumab infusion.

Epacadostat compliance will be calculated based on the drug accountability documented and monitored by the site staff (tablet counts and pill diary). The objective is 100% compliance and investigators and their staff should evaluate compliance at each visit, and take appropriate steps to optimize compliance. If the subject falls below 85% compliance, based on 2 subsequent visits,

then it will need to be addressed immediately, and could be means to remove the subject from the study.

Epacadostat will be given daily in combination with pembrolizumab every 3 weeks for up to 24 months provided subjects are receiving benefit from treatment and have not had disease progression or met any criteria for study withdrawal. Intrasubject escalation of epacadostat is not permitted. Single agent epacadostat may be continued beyond 24 months provided the patient has benefit.

Subjects will receive treatment in continuous 21 day cycles; however, treatment may include temporary interruptions to allow for resolution of certain toxicities. Interruptions from the protocol-specified treatment plan for > 12 weeks between epacadostat and pembrolizumab doses due to toxicity require consultation between Merck/Incyte and the investigator and written documentation of the collaborative decision on subject management.

4.4.2.2. **Pembrolizomab (MK-3475)**

Pembrolizumab 200 mg will be administered as a 30-minute intravenous (IV) infusion every 3 weeks (± 3 days) and will make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes -5 min/+10 min).

Pembrolizumab may be administered through a peripheral line or indwelling catheter. Intrasubject dose escalation of pembrolizumab is not permitted.

The total volume of study treatment infused will be compared to the total volume prepared to determine compliance with each dose administered.

Whenever possible, the lowest infusion rate should be used that will allow completion of the infusion within 30 minutes. Maximum rate should not exceed 6.7 mL/min through a peripheral line or indwelling catheter, however when necessary to infuse a larger volume (i.e. 250 mL), the flow rate may go as high as 10 ml/min (maximum) in order to keep the infusion within the window as defined above. Use 30 mL normal saline to flush the infusion line at the end of the infusion. Do not co-administer other drugs through the same infusion line.

See Appendix F which contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

4.5. **End of Treatment**

If a decision is made that the subject will permanently discontinue study drug, the end of treatment visit should be conducted approximately 30 days after the last dose of study medication.

When a subject discontinues/withdraws prior to study completion, all applicable activities scheduled for the final study visit should be performed at the time of discontinuation. Any AEs which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7. Subjects who a) attain a CR or b) complete 24 months of treatment with pembrolizumab and epacadostat may discontinue treatment with the option of restarting treatment in the future if/when they meet the criteria specified in Section 4.8. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 4.6.1) and then proceed to the Follow-Up Period of the study (described in Section 4.6.2).

4.6. **Follow-Up Phase**

4.6.1. **Safety Follow-Up Visit**

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of study treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 30 days of the final dose on the study or before initiation of a new anti-cancer treatment should also be followed and recorded. Subjects who are eligible for retreatment with pembrolizumab (as described in Section 4.8) may have up to two safety follow-up visits, one after the Treatment Period and one after the Second Course Phase.

4.6.2. **Follow-Up Period**

Subjects who discontinue study treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 9 weeks (± 7 days) by radiologic

imaging to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study or if the subject begins retreatment with pembrolizumab as detailed in Section 4.8, Second Course Phase. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

Subjects who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 4.8, Second Course Phase (Retreatment Period), will move from the Follow-up Phase to the Second Course Phase when they experience disease progression.

4.6.3. Survival Follow-Up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted by telephone every 12 weeks (~ 3 months) to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

4.7. Unscheduled Visits

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

4.8. Second Course Phase

Subjects who stop pembrolizumab and epacadostat with SD or better may be eligible for up to one year of additional pembrolizumab and epacadostat therapy if they progress after stopping study treatment. 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 pembrolizumab and epacadostat after attaining an investigator-determined confirmed CR according to RECIST 1.1, and
        - Was treated for at least 24 weeks with pembrolizumab before discontinuing therapy.
        - Received at least two cycles of treatment with pembrolizumab and epacadostat beyond the date when the initial CR was declared.

OR

- Had SD, PR or CR and stopped pembrolizumab and epacadostat treatment after 24 months of study therapy for reasons other than disease progression or intolerability.

AND

- Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with pembrolizumab
- Did not receive any anti-cancer treatment since the last dose of pembrolizumab
- Has an ECOG performance status of 0 or 1
- Demonstrates adequate organ function as defined by the eligibility criteria Section 3.3.
- Female subject of childbearing potential should have a negative serum or urine pregnancy test within 3 days 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. 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 therapy through 120 days after the last dose of study therapy.
- 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 study or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

Subjects who restart treatment will be retreated at the same dose and dose interval as when they last received pembrolizumab and epacadostat. Treatment will be administered for up to one additional year. Visit requirements are outlined in Section 9, schedule of events calendar.

4.9. Study Assessments and Procedures

4.9.1. Safety Assessments

4.9.1.1. Adverse Events

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the schedule of events calendar 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 5. Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to study treatment.

Please refer to Section 7 for detailed information regarding the assessment and recording of AEs.

Adverse events will be monitored from the time the subject begins treatment. Subjects will be instructed to report all AEs during the study and will be assessed for the occurrence of AEs throughout the study. In order to avoid bias in eliciting AEs, subjects will be asked general, non-leading questions such as "How are you feeling?" All AEs (serious and nonserious) must be recorded on the source documents and eCRFs regardless of the assumption of a causal relationship with the study drug. The definition, reporting, and recording requirements for AEs are described in Section 7.

All AEs of unknown etiology associated with epacadostat and pembrolizumab exposure should be evaluated to determine if it is possibly an AE of a potentially immunologic etiology. See Section 7 regarding the identification, evaluation, and management of AEs of potential immunological etiology.

Events of clinical interest (ECI) identified after signing consent through 100 days following cessation of treatment, regardless of initiation of new anticancer therapy, must be reported to Merck and Incyte within 10 days of the event.

Subjects should be assessed for possible ECIs prior to each dose. Laboratory results should be evaluated and subjects should be asked for signs and symptoms suggestive of an irAE. Subjects who develop an ECI 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

ECI, 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.

4.9.1.2. Comprehensive Physical Examination

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed during screening,

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

4.9.1.3. Targeted Physical Examination

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

4.9.1.4. Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of pembrolizumab treatment, and at treatment discontinuation as specified in the schedule of events calendar (Section 9). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be collected at Cycle 1 Day 1 only.

4.9.1.5. Twelve-Lead Electrocardiograms (ECGs)

Baseline ECG will be obtained during screening period prior to the first dose of epacadostat. Subsequent ECGs will be obtained as clinically indicated and at EOT. Clinically significant

abnormal findings prior to beginning therapy should be recorded as medical history. Clinically significant abnormal findings after beginning therapy or changes from baseline should be recorded as AEs.

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

4.9.1.6. Laboratory Assessments

Details regarding specific laboratory procedures/assessments to be performed in this study are provided below (hematology, chemistry and urinalysis). Laboratory tests should be conducted up to 2 days prior to dosing. If laboratory tests at screening are done within 7 days of Cycle 1 Day 1 they do not need to be repeated at that visit. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of study treatment.

Hematology, Lipid Panel, Coagulation Panel, Serology, and Endocrine Function Testing

Hematology, lipid panel, coagulation panel, and endocrine function will all be analyzed by the site laboratory prior to beginning treatment. Any subjects on coumadin-based anticoagulants that need weekly INR monitoring for the first 4 weeks with initiation of treatment will perform the INR testing locally. These labs should be drawn as 12 hour fasting. See Table 2 for more details about specific tests that need to be collected.

Tumor tissue sample molecular testing

Tumor molecular profiling will be performed on archival or newly obtained tumor tissue. These tests can be historical or obtained during the course of the study.

Urinalysis

Urinalysis will be analyzed by the site laboratory.

Serum Chemistry and Liver Function Tests

All serum chemistry testing (screening, Cycle 1 Day 1, and Day 1 of each cycle) will be performed fasting by the site's laboratory, as well as any additional LFT monitoring if it is required. Liver function test monitoring for persistent low-grade abnormalities does not need to be monitored twice a week indefinitely. Appropriate LFT monitoring intervals should be discussed with Merck and Incyte for these circumstances.

Pregnancy Testing

Serum or urine pregnancy tests will be analyzed by the site laboratory during screening and must be within 3 days before first dose of study treatment. Subsequently, pregnancy tests will be conducted only as medically indicated.

If a subject inadvertently becomes pregnant while on treatment with epacadostat and pembrolizumab, the subject will immediately be withdrawn from the study. The site will contact the subject at least monthly and document the subject's status until the first well-baby visit to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. The outcome of the pregnancy will be reported without delay and within 24 hours if the outcome is an SAE (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. If a male subject impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy reported and followed as described above and in Section 7.

Table 2: Required Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	PT/INR
Platelet count	Alanine aminotransferase (ALT)	Protein	aPTT
White Blood Cell Count (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	Total triiodothyronine (T3) (if applicable)
Red Blood Cell Count	Lactate dehydrogenase	Urine pregnancy test †	Free thyroxine (T4) (if

Hematology	Chemistry	Urinalysis	Other
	(LDH)		applicable)
Absolute Neutrophil Count	Carbon Dioxide *(CO_2 or bicarbonate)*		Thyroid stimulating hormone (TSH)
Absolute Lymphocyte Count			Blood for correlative studies and future research
	Uric Acid		
	Calcium		
	Chloride		
	Glucose		
	Phosphorus		
	Potassium		
	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.			

4.9.2. Efficacy Assessments – Tumor Imaging During the Study

Initial tumor imaging must be performed within 28 days before the first planned dose of study treatment. The site study team must review pre-study images to confirm the subject has measurable disease per RECIST v1.1 for solid tumors and irRC. A standard, full assessment for lesions should be conducted at baseline, including CT or MRI scans of chest, abdomen, and pelvis for solid tumors. The same modality (CT and/or MRI) should be used for follow-up assessments every 9 weeks, including radiological assessments of all sites of disease present at baseline unless otherwise medically indicated. In addition to radiological monitoring, all other lesions observed at the screening visit should be followed. Baseline scan must be a contrast computed tomography (CT) with contrast of the chest/abdomen/pelvis, except in circumstances where there is a contrast allergy.

Tumor imaging may be performed by CT and/or MRI, but investigator should do their best, as medically appropriate, to keep with the same imaging technique per subject throughout the

study. Scans must be a contrast CT and/or MRI, except in circumstances where there is a contrast allergy. Imaging should be performed every 9 weeks (± 7 days) or more frequently if clinically indicated. Imaging should not be delayed for delays in cycle starts or extension of combination treatment cycle intervals.

Per irRC, response should be confirmed by a repeat radiographic assessment not less than 4 weeks from the date the response was first documented. The scan for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan (9 weeks later), whichever is clinically indicated.

Imaging should continue to be performed until documented disease progression, the start of new anticancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs first. Disease progression should be confirmed at least 4 weeks after the first scan indicating progressive disease in clinically stable subjects. Subjects who have unconfirmed disease progression may continue on treatment until progression is confirmed provided they have met the conditions detailed in Section 10.

4.9.3. **Tumor Biopsy**

Fresh tumor biopsies (defined as a biopsy specimen taken since completion of the most recent prior chemotherapy regimen) will be required at baseline and on treatment of the same lesion (day 42 +/- 5 days). Patients are not required to have PD-1 expression testing for enrollment on the study. All sites of disease that are amendable to biopsy are allowable per protocol. Measurable lesions that are the only site of measurability per RECIST v1.1 cannot be biopsied due to obstruction of measurement. Additionally, previously irradiated lesions cannot be biopsied due to potential for necrotic and nonviable tissue.

Standard techniques will be used for all biopsies, which may include CT, ultrasound, or endoscope depending on site of biopsiable lesion. The sample should be obtained as core or endoscopic. Fine needle aspirations (FNA) samples are acceptable. The total number of core biopsies obtained should be approximately 6-15, with an average of 10.

4.9.4. Performance and Quality of Life Assessments

4.9.4.1. Eastern Cooperative Oncology Group Performance Status

The investigator or qualified designee will assess ECOG performance status (Appendix C) at screening, prior to the administration of each dose of study treatment and discontinuation of study treatment as specified in the schedule of events calendar (Section 9).

4.10. General Concomitant Medication and Supportive Care Guidelines

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

4.10.1. 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 CRF.

All concomitant medications received within 28 days before the first dose of study treatment and 30 days after the last dose of study treatment should be recorded. Concomitant medications administered for 30 days after the last dose of study treatment should be recorded for SAEs. Bone protectants (bisphosphonates and denosumab) are allowed for treatment of bone metastases while patients are on the study.

4.10.2. Restricted Medications

Low-dose Coumadin (1 mg) is acceptable; however, standard dose levels of Coumadin are prohibited given fluctuations in INR.

4.10.3. Prohibited Medications

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

- Antineoplastic systemic chemotherapy or biological therapy
- Any immunological-based treatment for any reason
- Investigational medications other than pembrolizumab or epacadostat
- Radiation therapy
  - Note: Palliative radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- Live vaccines within 30 days prior to 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, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology.
- Any melatonin supplements.
- Any MAOI or drug associated with significant MAO inhibitory activity agents is prohibited from 21 days before Day 1 through 2 weeks after the final dose of INCB024360 has been taken (see 14.3).
- Any UGT1A9 inhibitor, including: acitretin, amitriptyline, androsterone, cyclosporine, dasatinib, diclofenac, diflunisal, efavirenz, erlotinib, estradiol (17-beta), flutamide, geftinib, gemfibrozil, glycyrrhetinic acid glycyrrhizin, imatinib, imipramine, ketoconazole, linoleic acid, mefenamic acid, mycophenolic acid,

niflumic acid, nilotinib, phenobartital, phenylbutazone, phenytoin, probenecid, propofol, quinidine, ritonavir, Sorafenib, sulfinpyrazone, valproic acid, and verapmil.

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

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

4.10.4. Supportive Care Guidelines and Handling Immune Related AEs

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined below in section 6.2. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab and/or epacadostat. If after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below). It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

Pembrolizumab may cause severe or life threatening infusion-reactions. 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 3.

Table 3: Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing

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 hours	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDS • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within 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 study treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg orally (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg orally (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	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further study treatment administration.**	
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

- Nausea/vomiting: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Subjects should be strongly encouraged to maintain liberal oral fluid intake.
- Anti-infectives: Subjects with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.

4.11. Diet/Activity/Other Considerations

4.11.1. Diet

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

4.11.2. Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm. For this study, 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) 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 study drug and for 120 days after the last dose of study drug by complying with one of the following:

(1) practice abstinence[†] from heterosexual activity;

OR

(2) 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

- contraceptive rod implanted into the skin

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

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

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 study 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.

4.11.3. Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab and/or Epacadostat, the subject will immediately be removed from the study. 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 Merck and Incyte without delay 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 Merck and Incyte. If a male subject impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy reported to Merck and Incyte and followed as described.

4.11.4. Use in Nursing Women

It is unknown whether pembrolizumab nor Epacadostat 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 breast-feeding are not eligible for enrollment.

4.12. Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the study at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the study is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

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

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed radiographic disease progression

  Note: For unconfirmed radiographic disease progression, please see Section 10.

  Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved
- Unacceptable adverse experiences
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- The subject is lost to follow-up
- Completed 24 months of uninterrupted treatment with pembrolizumab or 35 administrations of study medication, whichever is later.

  Note: 24 months of study medication is calculated from the date of first dose. Subjects

who stop pembrolizumab after 24 months may be eligible for up to one year of additional study treatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 4.8.

- Administrative reasons

The EOT and Follow-up visit procedures are listed in Section 9 (Study Calendar) and Section 4 (Visit Requirements). After the end of treatment, each subject will be followed up to 30 days or until new anti-cancer treatment is initiated, whichever occurs first for adverse event monitoring, including SAEs. Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

4.12.1. Discontinuation of Study Therapy after Complete Response

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 weeks with pembrolizumab and epacadostat and had at least two treatments with pembrolizumab beyond the date when the initial CR was declared. Subjects who then experience radiographic disease progression may be eligible for up to one year of additional treatment with pembrolizumab and epacadostat via the Second Course Phase at the discretion of the investigator if no cancer treatment was administered since the last dose of pembrolizumab, the subject meets the safety parameters listed in the inclusion and exclusion criteria, and the study is open. Subjects will resume therapy at the same dose and schedule at the time of initial discontinuation.

4.12.2. Noncompliance with Oral Epacadostat Dosing

Each patient will be given an oral medication diary to take home and record the dosing information including times of day and number of pills taken to ensure they are taking the medication as prescribed at home. Compliance of > 85% based on pill reconciliation and home diary entries at ≥ 2 consecutive visits will be strongly encouraged.

5. INVESTIGATIONAL AGENT/DEVICE/PROCEDURE INFORMATION

5.1. Investigational Products Description

Detailed pharmaceutical and therapeutic background of pembrolizumab and epacadostat is provided in the respective IBs. 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 products in accordance with the protocol and any applicable laws and regulations.

5.1.1. Epacadostat

5.1.1.1. Packaging, Labeling, and Preparation

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

5.1.1.2. Storage and Stability

Clinical supplies of epacadostat should be stored under ambient conditions, between 15°C to 30°C (59°F to 86°F). Study drug must be stored in a locked storage area with limited access. If epacadostat is exposed outside of the defined temperature ranges please quarantine the affected bottles and complete and submit the Temperature and Light Excursion Form (Appendix G) to Incyte according to the instructions on the form. Incyte will provide guidance as to whether the bottles will need to be destroyed based on the information that has been provided on the form.

If epacadostat is exposed outside of the defined temperature ranges please quarantine the affected bottles and complete and submit the Temperature and Light Excursion Form (Appendix G) to Incyte according to the instructions on the form. Incyte will provide guidance as to

whether the bottles will need to be destroyed based on the information that has been provided on the form.

5.1.2. Pembrolizumab

5.1.2.1. Packaging, Labeling, and Preparation

Clinical supplies will be provided by Merck and will be affixed with a clinical label in accordance with regulatory requirements.

Details on preparation and administration of pembrolizumab (MK-3475) are provided in the Appendix F.

Product Name & Potency	Dosage Form
Pembrolizumab 100 mg/ 4mL	Solution for Injection

5.1.2.2. Storage and Stability

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

Open-label vials of pembrolizumab should be stored between 2°C to 8°C (36°F to 46°F) in a locked storage area protected from light with limited access. Vials should be stored in the original box to ensure the drug product is protected from light. A maximum 12 hours of light exposure is permitted for the pembrolizumab vials.

Pembrolizumab solutions may be stored at room temperature for a cumulative time of up to 4 hours. This includes room temperature storage of drug product solution in vial, room temperature storage of admixture solution in the IV bags and the duration of infusion.

IV bags containing pembrolizumab may be stored under refrigeration at 2°C to 8°C (36°F to 46°F) for up to 20 hours. If refrigerated, allow the IV bags to come to room temperature prior to use.

5.2. **Accountability, Handling, and Disposal of Epacadostat and Pembrolizumab**

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

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

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

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

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

Completed accountability records will be archived by the site. At the completion of the study, the investigator or designee will oversee destruction according to institutional standard operating procedures.

The investigator is responsible for keeping accurate records of the clinical supplies received from Merck or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the study.

Upon completion or termination of the study, all unused and/or partially used pembrolizumab will be destroyed at the site per institutional policy. It is the investigator's responsibility to

arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

6. DOSE MODIFICATIONS

6.1. Rationale for Dose Modification(s)

Subjects may require modification of epacadostat if necessitated by drug-related AEs, including irAEs; dose reductions of pembrolizumab are prohibited.

Epacadostat Dose Level Table	
Dose Level	**Dose in mg**
Starting Dose (0)	300mg BID
First Dose Reduction (-1)	200mg BID
Second Dose Reduction (-2)	100mg BID

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks (~ 21 days) of the scheduled interruption, unless otherwise discussed with Merck and Incyte. The reason for interruption should be documented in the patient's study record.

In some circumstances, it may be necessary to temporarily interrupt both study treatments as a result of AEs that may have an unclear relationship to study drug(s). Treatment with both study drugs should be withheld for drug-related Grade 4 hematologic toxicities, non-hematological toxicity ≥ Grade 3 (including laboratory abnormalities), and severe or life-threatening AEs.

6.2. Dose Modifications of Pembrolizumab and Epacadostat

AEs (both non-serious and serious) associated with pembrolizumab and epacadostat exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Based on existing clinical trial data, most irAEs were reversible and could be managed with interruptions of pembrolizumab and

epacadostat, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and epacadostat and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in **Table 4**.

See Sections 4.10.4 for additional supportive care guidelines, including use of corticosteroids if necessary. Patients requiring treatment with corticosteroids for irAEs should be held through completion of taper, unless otherwise discussed and approved by Merck and Incyte.

In case toxicity does not resolve to Grade 1 within 12 weeks after last dose of study treatment should be discontinued only after consultation with Merck and Incyte. With investigator and Merck and Incyte agreement, subjects with a laboratory AE still at Grade 2 after 12 weeks may continue treatment in the study only if asymptomatic and controlled.

General Instructions for management of irAE

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 has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. For subjects with Grade 3 or 4 immune-related endocrinopathy, pembrolizumab may be resumed when AE improves to Grade 2 or lower and is controlled with hormonal replacement therapy.
3. For situation where pembrolizumab is withheld initially, pembrolizumab 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. However, subjects with asymptomatic
4. 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

Table 4: Dose Modification Guidelines for Drug Immune-Related AEs associated with epacadostat and pembrolizumab

General instructions for AEs associated with Pembrolizumab:

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 has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab 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.

The below table represents guidelines and are not required management for immune-related AEs and can be implemented at the discretion of the investigator. Specialist referral (Endocrinology, Pulmonary, GI, etc) is encouraged if questions arise about appropriate management.

Note: Unless listed below, Grade 1 for all disease groups: continue therapy, treat symptoms, close monitoring for worsening symptoms, educate patient to report worsening immediately, if worsens: Treat as Grade (G) 2 or 3/4.

Toxicity	Hold Treatment For Grade	Management + Timing for Restarting Treatment	Follow-up	Treatment Discontinuation
Type 1 diabetes mellitus (if new onset) or Hyperglycemia[1]	**Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**	- Delay therapy for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure. - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria. - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide. - Resume therapy when patients are clinically and metabolically stable	_____	Discontinue Pembrolizumab and Epacadostat if not clinically and metabolically stable
Hyperthyroidism[1]	**Grade 2**	- Continue therapy. - Non-selective beta blockers (e.g. propranolol) are suggested as initial therapy.	_____	_____
	Grade 3	- Delay therapy - Resume therapy with one dose reduction when toxicity resolves to Grade 0-1 -Treat with non-selective beta-blockers or thionamides as appropriate - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.	_____	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks

		-Consider endocrine consult		
	Grade 4	- Discontinue therapy permanently. - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. - Consider endocrine consult	_____	Permanently discontinue
Hypothyroidism[1]	**Grade 2-4**	- Continue therapy at same doses. - Thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care. -Consider endocrine consult for Grade 3-4	_____	Discontinue Pembrolizumab and Epacadostat if not clinically and metabolically stable
Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders				
Hypophysitis	**Grade 2**	- Delay therapy - 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent and initiate hormonal replacement as clinically indicated - Can resume once metabolically and clinically stable and on doses of steroids < 10mg/day prednisone equivalent. - Consult endocrinology for all grades	_____	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	Grades 3-4	- Discontinue therapy permanently.	_____	Permanently discontinue

Suspicion of adrenal crisis (e.g. severe dehydration, hypotension, shock out of proportion to current illness[1]		- Delay therapy - Rule out sepsis - Stress dose of IV steroids with mineralocorticoid activity - IV fluids - Consult endocrinologist - If adrenal crisis ruled out, then treat as above for symptomatic endocrinopathy. - Can resume once metabolically and clinically stable and on doses of steroids < 10mg/day prednisone equivalent.	_____	_____
Diarrhea/Colitis[1]	**Grade 2** Diarrhea: 4-6 stools/day over baseline; IV fluids indicated < 24 hours (hrs); not interfering with ADL. Colitis: abdominal pain; blood in stool	-Delay therapy for 5-7 days and reevaluate. -Resume therapy with same dose when toxicity resolves to Grade 0-1 -Symptomatic treatment -Drink liberal liquids if not feasible administer fluids via IV infusion	**If improves for to grade 1:** - Resume therapy with same dose **If persists > 5-7 days or recur:** - 1.0-2.0 mg/kg/day methylprednisolone or oral equivalent - When symptoms improve to grade 1, taper steroids over at least 4 weeks, consider prophylactic antibiotics for opportunistic infections, and resume therapy. **If worsens or persists >3-5 days with oral steroids:** - Treat as Grade 3/4	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks

	Grade 3 Diarrhea: >7 stools/day over baseline; IV fluids ≥24 hrs; interfering with ADL. Colitis: severe abdominal pain, medical intervention indicated, peritoneal signs	- Delay therapy for 3-5 days and reevaluate. -Resume therapy with one dose reduction when toxicity resolves to Grade 0-1. - 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent. - Add prophylactic antibiotics for opportunistic infections - Consider lower endoscopy -Drink liberal liquids if not feasible administer fluids via IV infusion	**If improves:** - Continue steroids until grade 1, then taper over at least 4 weeks. **If persists > 3-5 days, or recurs after improvement:** - GI referral, and consideration of Infliximab 5 mg/kg under supervision by gastroenterologist (if no contraindication) Note: Infliximab should not be used in cases of perforation or sepsis	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	Grade 4 life-threatening, perforation	- Discontinue therapy permanently. - 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent. - Add prophylactic antibiotics for opportunistic infections - Consider lower endoscopy -Drink liberal liquids if not feasible administer fluids via IV infusion	**If improves:** - Continue steroids until grade 1, then taper over at least 4 Weeks. **If persists > 3-5 days, or recurs after improvement:** - GI referral, and consideration of Infliximab 5 mg/kg under supervision by gastroenterologist (if no contraindication) Note: Infliximab should not be used in cases of perforation or sepsis	Permanently discontinue
AST, ALT, or Increased Bilirubin[1]	**Grade 1** AST or ALT > ULN TO 3.0 x ULN and/or T. bili > ULN - 1.5 x ULN	- Continue therapy	- Continue liver function tests (LFT) monitoring per protocol	
	Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and/or T. bili > 1.5 to 3 x ULN	- Delay therapy for 5-7 days and reevaluate. - Resume therapy with same dose when toxicity resolves to Grade 0-1	**If returns to baseline:** - Resume routine monitoring, resume therapy same dose. **If elevation persist > 5-7 days or worsen:**	Toxicity does not resolve within 12 weeks of last dose

		- Increase frequency of monitoring to every 3 days.	- 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, a steroid taper should be started and continued over no less than 4 weeks, consider prophylactic antibiotics for opportunistic infections, and resume therapy with same dose.	
	Grade 3-4 AST or ALT > 5 x ULN and/or T. bili > 3 x ULN	- Discontinue therapy permanently (see exception below)[a] (Therapy may be delayed rather discontinued if AST/ALT ≤ 8 x ULN and T.bili ≤ 5 x ULN) - Increase frequency of monitoring to every 1-2 days - 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent (The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV) - Add prophylactic antibiotics for opportunistic infections - Consult gastroenterologist	**<u>If returns to grade 2</u>:** - Taper steroids over at least 4 weeks **<u>If does not improve in > 3-5 days, or worsens or rebounds</u>:** - Add mycophenolate mofetil 1g twice daily (BID) - If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines.	Permanently discontinue
Neurological[1]	**Grade 2** Moderate symptoms; Limiting instrumental ADL	- Delay therapy. - Resume therapy with same dose when toxicity resolves to Grade 0-1 - Treat symptoms per local guidelines - Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or PO equivalent. -If ≥ Grade 2 Neurologic AE consider Neurology consult and brain imaging	**<u>If improves to baseline</u>:** - Resume therapy with same dose when toxicity resolves to Grade 0-1 **<u>If worsens</u>:** - Treat as Grade 3-4	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
		- Discontinue therapy	**<u>If improves to grade 2</u>:**	Permanently discontinue

	Grade 3-4 Severe symptoms; Limiting self-care ADL; Life-threatening	- If ≥ Grade 2 Neurologic AE consider Neurology consult and brain imaging - Treat symptoms per local guidelines - 1.0-2.0 mg/kg/day IV methylprednisolone or IV equivalent - Add prophylactic antibiotics for opportunistic infections	- Taper steroids over at least 4 weeks **<u>If worsens or atypical presentation</u>:** - Consider IVIG or other immunosuppressive therapies per local guidelines.	
Pneumonitis[1]	**Grade 1** Radiographic changes only	- Consider delay of therapy - Monitor for symptoms every 2-3 days - Consider Pulmonary and Infectious Disease (ID) consults	- Re-image at least every 3 weeks	_____
	Grade 2 Mild to moderate **new symptoms**	- Delay therapy -Resume therapy with same dose when toxicity resolves to Grade 0-1 - For recurrent Grade 2 Pneumonitis **discontinue therapy** - Pulmonary and ID consults - Monitor symptoms daily, consider hospitalization - 1.0-2.0 mg/kg/day methylprednisolone IV or oral equivalent, followed by taper - Add prophylactic antibiotics for opportunistic infections - Consider bronchoscopy, lung biopsy	- Re-image every 1-3 days **<u>If improves</u>:** - When symptoms return to near baseline, taper steroids over at least 4 weeks and then resume therapy with same dose and consider prophylactic antibiotics **<u>If not improving after 2 weeks or worsening</u>:** - Treat as Grade 3-4	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	Grade 3-4	- Discontinue therapy	**<u>If improves to baseline</u>:** - Taper steroids over at least 6 weeks	Permanently discontinue

	Severe new symptoms; New/worsening hypoxia; Life-threatening	- Hospitalize - Pulmonary and ID consults - 2-4 mg/kg/day methylprednisolone IV or IV equivalent - Add prophylactic antibiotics for opportunistic infections - Consider bronchoscopy, lung biopsy	**<u>If not improving after 48 hours or worsening</u>:** - Add additional immunosuppression (e.g. infliximab, cyclophosphamide, intravenous immunoglobulin (IVIG), or mycophenolate mofetil).	
Renal Failure or Nephritis[1]	**Grade 1** Creatinine > ULN and > than baseline but ≤ 1.5 x baseline	- Continue therapy - Monitor creatinine weekly	**<u>If returns to baseline</u>:** - Resumes routine creatinine monitoring per protocol	_____
	Grade 2 Creatinine > 1.5 x baseline to 3.0 x ULN	- Delay therapy -Resume therapy with same dose when toxicity resolves to Grade 0-1 - Monitor Creatinine every 2-3 days - 1.0 -2.0 mg/kg/day methylpredniolone IV or oral equivalent. - Consider renal biopsy	**<u>If returns to Grade 1</u>:** - Taper steroids over at least 4 weeks, consider prophylactic antibiotics for opportunistic infections, and resume therapy with same dose and routine creatinine monitoring. **<u>If elevations persist > 7 days or worsen</u>:** - Treat as Grade 4	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	Grade 3-4 Creatinine > 3 x baseline to > 6 x ULN	- Discontinue therapy permanently - Monitor Creatinine daily - 1.0-2.0 mg/kg/day methylpredniolone IV or IV equivalent - Consult nephrologist - Consider renal biopsy	**<u>If returns to grade 1</u>:** - Taper steroids over at least 4 weeks and add prophylactic antibiotics for opportunistic infections.	Permanently discontinue

Skin[1]	**Grade 1** Covering < 10% body surface area (BSA)*	- Continue therapy - Symptomatic therapy (e.g. antihistamines, topical steroids)	**<u>If persists > 1-2 weeks or recurs</u>:** - Continue therapy - Consider skin biopsy - Consider 0.5-1.0 mg/kg/day methylprednisolone IV or oral equivalent. Once improving, taper steroids over at least 4 weeks, consider prophylactic antibiotics for opportunistic infections.	_____
	Grade 2 Covering 10-30% BSA*	- Symptomatic therapy (e.g. antihistamines, topical steroids) -Delay therapy for 1-2 weeks and reevaluate. -Resume therapy with same dose when toxicity resolves to Grade 0-1	**<u>If persists > 1-2 weeks or recurs</u>:** - Consider skin biopsy - Delay therapy - Consider 0.5-1.0 mg/kg/day methylprednisolone IV or oral equivalent. Once improving, taper steroids over at least 4 weeks, consider prophylactic antibiotics for opportunistic infections, and resume therapy with same dose **<u>If worsens</u>:** - Treat as Grade 3-4	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	Grade 3 Covering > 30% BSA	- Delay treatment and consider oral steroids if necessary. - Resume therapy with one dose reduction when toxicity resolves to Grade 0-1 - If the rash is grade 3 only based on BSA, and is otherwise mild and responds to dose interruption and topical steroids, can consider resuming at the same dose. - Consider skin biopsy	**<u>If improves to grade 1</u>:** - Taper steroids over at least 4 weeks and add prophylactic antibiotics for opportunistic infections - Resume therapy with one dose reduction when toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks

		- Dermatology consult - 1.0-2.0 mg/kg/day IV methylprednisolone or IV equivalent		
	Grade 4 Any % BSA; Life-threatening consequences (Refer to NCI CTCAE v5 for term-specific grading criteria)	- Discontinue therapy permanently - Consider skin biopsy - Dermatology consult - 1.0-2.0 mg/kg/day IV methylprednisolone or IV equivalent	Permanently discontinue	Permanently discontinue
Myocarditis	**Grade 1 or 2**	- Delay therapy - Administer corticosteroids	_____	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	Grade 3 or 4	- Discontinue therapy permanently - Administer corticosteroids	Permanently Discontinue	Permanently Discontinue
All Other Drug-Related Toxicity[c]	**Grade 3 or Severe (meeting SAE criteria) or intolerable/ persistent Grade 2**	- Delay therapy -Resume therapy with same dose when toxicity resolves to Grade 0-1 - Based on severity of AE administer corticosteroids - If an SAE, consider dose reduction. - Ensure adequate evaluation to confirm etiology or exclude other causes	_____	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	Grade 4 or recurrent Grade 3	- Permanently discontinue - Based on severity of AE administer corticosteroids	_____	Permanently discontinue

		- Ensure adequate evaluation to confirm etiology or exclude other causes		

Note: Permanently discontinue for any severe (meeting SAE criteria) or Grade 3 drug-related AE that recurs or any life-threatening event.

1. In general, for disease group GI, Hepatic, Endocrinopathy, Pulmonary, Renal, Neurological and skin:

- Rule out non-inflammatory causes. If non-inflammatory causes are identified, treat accordingly and continue I-O therapy.
- Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

For the below disease groups, also:

- For Endocrinopathy AE management:
  Consider visual field testing, endocrinology consultation, and imaging.
- For GI AE management:
  Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.
- For Hepatic AE management:
  Consider imaging for obstruction.
- For Pulmonary AE management:
  Evaluate with imaging and pulmonary consultation.
- For Renal AE management:
  Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

[a] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.
[b] 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 pre-medicated for the next scheduled dose.
[c] Patients with intolerable or persistent Grade 2 drug-related AE may delay study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 AEs for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

Table 5: Dose Modification Guidelines for Non-immune Drug-Related Adverse Events

Toxicity	Grade	Hold Treatment (Y/N)	Timing for Treatment Restart	Dose/Schedule for Treatment Restart		Discontinue Subject (After Consultation with Merck & Incyte)
				Epacadostat (INCB024360)	Pembrolizumab (MK-3475)	
Hematologic toxicity	1, 2	No	N/A	N/A	N/A	N/A
	3	Yes	Toxicity resolves to ≤ Grade 1 or baseline	First occurrence, restart at same dose. Second occurrence or more, reduce dose when resuming.	Restart at same dose and schedule. See Sections 4.10.4. and 6.3. for recommendations regarding immune-mediated AEs.	Toxicity does not resolve within 12 weeks of last infusion.
	4	Yes	N/A	N/A	N/A	Permanently discontinue
Non-hematologic toxicity, excluding immune related AEs in Table 4 Note: Exception to be treated to similar Grade 1 toxicity: • Grade 2 alopecia • Grade 2 fatigue • Grade 3 rash in the absence of desquamation, no mucosal involvement, does not require	1	No	N/A	N/A	N/A	N/A
	2	Consider holding for persistent symptoms	Toxicity resolves to ≤ Grade 1 or baseline	Reduce 1 dose level	Restart at same dose and schedule. See Sections 4.10.4. and 6.3. for recommendations regarding immune-mediated AEs.	Toxicity does not resolve within 12 weeks of last infusion
	3	Yes	Toxicity resolves to ≤ Grade 1 or baseline	Reduce 1 dose level	Restart at same dose and schedule. See Sections 4.10.4. and 6.3. for recommendations regarding immune-mediated AEs.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks

Toxicity	Grade	Hold Treatment (Y/N)	Timing for Treatment Restart	Dose/Schedule for Treatment Restart		Discontinue Subject (After Consultation with Merck & Incyte)
				Epacadostat (INCB024360)	Pembrolizumab (MK-3475)	
systemic steroids, and resolves to Grade 1 within 14 days For additional information regarding AE with potential immune etiology, see Sections 4.10.4 and 6.3.	4	Yes	N/A	N/A	N/A	Permanently discontinue

Note: Subjects who experience a recurrence of the same severe or life-threatening AE at the same grade or greater with re-challenge of the combination should be discontinued from study treatment immediately and not re-challenged.

6.3. **Management of Immune-Related Adverse Events (irAEs)**

Events of clinical interest of a potential immunologic etiology or irAEs may be defined as an AE of unknown etiology, associated with drug exposure and consistent with an immune phenomenon. irAEs may be predicted based on the nature of the pembrolizumab or epacadostat compounds, their mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. Special attention should be paid to AEs that may be suggestive of potential irAEs. An irAE can occur shortly after the first dose or several months after the last dose of treatment.

If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes before labeling an AE as an irAE. Subjects who develop a ≥ Grade 2 irAE should be discussed immediately with the sponsor. Please refer to Table 4 in Section 6.2.

6.4. **Procedures for Subjects Exhibiting Serotonin Syndrome (SS)**

There is a theoretical chance that epacadostat could cause an increase in serotonin levels in the brain that might trigger SS when administered in combination with other serotonergic agents. This syndrome has been most closely associated with use of MAOIs, Demerol®, linezolid, or methylene blue; all of these agents are prohibited during the study. Serotonin reuptake inhibitors (SSRIs) and serotonin/norepinephrine reuptake inhibitors (SNRIs) are permitted in the study. The following procedures will be implemented if subjects exhibit the signs/symptoms of SS including tremor; hyperreflexia; spontaneous, ocular, or inducible clonus; together with agitation, fever, diaphoresis, or muscle rigidity:

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

- If subject chooses to remain in the study, restart treatment with epacadostat after the SSRI or SNRI has been discontinued, no sooner than 5 half-lives have elapsed for the specific SSRI or SNRI in question, and after resolution of signs/symptoms of SS. The SSRI or SNRI dosing MAY NOT be restarted.
- If subject chooses to withdraw from the study, or must restart treatment with SSRI or SNRI, the subject should be scheduled for a follow-up visit. Treatment with SSRI or SNRI may be initiated 2 weeks after resolution of signs and symptoms of SS.

7. ADVERSE EVENTS AND REPORTING PROCEDURES

7.1. **Adverse Event Definition and Reporting**

An AE 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 unfavorable 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 Merck's product, is also an AE.

AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.

AEs will be graded according to NCI CTCAE v5. Both serious and non-serious AEs will be clearly noted in source documentation and listed on study specific eCRFs. The investigator or designee will assess each AE to determine whether it is unexpected according to the informed consent document, protocol document, or IBs, and related to the investigation. After the end of treatment, each subject will be followed up to 30 days or until new anti-cancer treatment is initiated, whichever occurs first for adverse event monitoring, including SAEs grade 3 and above, and all subsequent follow-up reports will be reported to the

Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) using the study specific eCRF regardless of the event's relatedness to the investigation. Events meeting the IRB definition of 'Unanticipated Problem' will be reported to the IRB within 10 working days of investigator determination expedited reporting is required, or within 5 working days for deaths or life-threatening experiences.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered AEs. 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.

Merck 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 Merck for human use.

Adverse events may occur during the course of the use of Merck product in clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal. Progression of the cancer under study is not considered an AE.

All AEs/SAEs that occur after the consent form has been signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the study, 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 initiation of a new anticancer therapy, all AEs must be reported by the investigator. Such events will be recorded at each examination on the AE eCRF. The reporting timeframe for AEs meeting any serious criteria is described in section 7.1. The investigator will make every attempt to follow all subjects with non-serious AEs for outcome.

Adverse events will not be collected for subjects during the pre-screening period (for determination of archival tissue status); subjects will begin AE collection after signing consent.

Epacadostat Adverse Event reporting:

1. Initial Serious Adverse events (SAEs) and/or subsequent follow-up reports should be reported via email to: ***IncytePhVOpsIST@incyte.com***. SAE reports should be for a single subject with any additional documents (i.e. discharge summary, relevant test results) included for the same subject as individual attachments to the email. One email can have multiple attachments as long as each attachment contains relevant information for the same subject.

2. Please email your SAE form with a cover sheet and any additional attachments to the IST email address: ***IncytePhVOpsIST@incyte.com.***

3. Telerx C3i is the PhV Clinical Research Organization (CRO) for Incyte. They will be contacting you for SAE follow-up requests and data clarifications by sending you a data clarification form (DCF). See follow-up section for details on this process. The following is general contact information for Telerx C3i.

   TELERX C3I (Incyte PhV CRO)
   US SAE fax number 1-866-726-9234

- **Initial reports**

Incyte needs to be notified within 24 hrs of learning of an event as well as providing a completed SAE form emailed to *IncytePhVOpsIST@incyte.com.*

1. SAE reporting for each subject begins the day patient start treatment and up to 30 days after subject has completed or discontinued from the study or until new anti-cancer treatment is initiated, whichever occurs first.

2. All SAE notices are sent from the site to Incyte via a central email address: ***IncytePhVOpsIST@incyte.com*** established for IST sites for this process.

3. SAEs, occurring using Incyte Study drug, are reported in accordance with the effective protocol. SAEs occurring with any another commercial drug are reported to manufacturer of that drug in accordance with regulations and protocol.

4. SAEs related to concomitant medications/drug delivery systems are reported directly to the manufacturers of those drugs/devices in accordance with the package insert. Meaning, follow the SAE manufacturer reporting requirements for all medication other than Epacadostat.

5. All SAE details are recorded on the SAE Report form, regardless of causality to the investigational product and sent via email in accordance with the protocol. If a non-serious Adverse Event (AE) becomes serious, the process for SAE reporting is followed.

6. Additional information requested upon internal Incyte review will be asked by Telerx C3i in the form of a Data Clarification Form (DCF).

- **Follow-up reports**

1. Follow-up SAE reports are sent via email to ***IncytePhVOpsIST@incyte.com*** from the Investigator site.

2. Telerx C3i tracks any critical outstanding follow-up items and questions and contacts the investigational site via a faxed DCF for the additional requested information until all outstanding queries are resolved. A sample of this form is included in Appendix III. This includes requests for hospital discharge summaries, autopsy reports, and death certificates (if applicable), results of relevant laboratory, and diagnostic tests. The investigational site faxes the additional information to Telerx C3i, using the Telerx C3i SAE fax number. The site personnel will update all relevant data on the appropriate SAE Report Form or equivalent to include any new or changed information. The Incyte Safety Representative (IC SR) will monitor outstanding queries and take appropriate action needed for resolution.

3. Any serious SAE upgraded to death or life-threatening requires that the follow up report be emailed to: ***IncytePhVOpsIST@incyte.com*** email address within 24 hours.

- **Regulatory Reporting**

The Investigator Sponsor (George A. Fisher, Jr., MD, PhD) of the IST trial is responsible for meeting expedited reporting requirements to Health Authorities and all participating investigators under their institution's IND. Incyte is responsible for meeting expedited reporting requirements to Health Authorities (HAs) in their respective territory and for cross reporting any Serious Unexpected Suspected Adverse Reaction (SUSAR) originating from IST sponsored studies to Incyte's IND, NDA, and Incyte investigators from Incyte sponsored trials as required.

- **Reporting of Pregnancy**

An "Initial Pregnancy Report" or equivalent must be completed in full and emailed to ***IncytePhVOpsIST@incyte.com*** within 24 hrs of discovery of a pregnancy of a subject who has taken the Incyte product or the pregnancy of a partner for a subject who has taken the Incyte product. The "Follow-up Pregnancy Report Form" or equivalent must be completed and emailed to ***IncytePhVOpsIST@incyte.com*** within 30 days after delivery, so that Incyte is provided with information regarding the outcome of the pregnancy. If the pregnancy results in any events which meet the serious criteria (i.e., miscarriage or termination), the SAE reporting process needs to be followed and the timelines associated with an SAE should be followed.

7.2. Definition of an Overdose for This Protocol and Reporting of Overdose - Pembrolizumab

For purposes of this study, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. Appropriate supportive treatment should be provided if clinically indicated. 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 a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Merck's product 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 within 24 hours to Merck Global Safety Attn: Worldwide Product Safety; FAX 215 993-1220)

7.3. Definition of an Overdose for This Protocol and Reporting of Overdose – Epacadostat

There has been no clinical experience with overdose of Epacadostat. Treatment of overdose should consist of general supportive measures.

7.4. Reporting of Pregnancy and Lactation to Merck and Incyte

Although pregnancy and lactation are not considered AEs, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the study.

Pregnancies and lactations 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 study, 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 that occur from the time of treatment allocation/randomization through 120 days following cessation of study product, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. 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 Merck Global Safety (Attn: Worldwide Product Safety; FAX 215 993-1220) AND Incyte (***IncytePhVOpsIST@incyte.com)***

7.5. Reporting of Adverse Events to Merck and Incyte

7.5.1. Serious Adverse Events

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

- Results in death;
- Is life threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically must have caused death if it were more severe);
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is another important medical event
- *Note:* The following hospitalizations are not considered SAEs:
    - A visit to the emergency room or other hospital department lasting less than 24 hours that does not result in admission (unless considered an "important medical event" or a life-threatening event).
    - Elective surgery planned before signing consent
    - Admission per protocol for planned medical/surgical procedure (e.g., mediport placement)
    - Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
    - Medical/surgical admission for purpose other than remedying ill health state that was planned before study entry. Appropriate documentation is required in these cases.
    - Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative)
- *Note:* In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Merck in the same

timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.

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

For the time period beginning when the consent form has been signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject must be reported to the FDA through appropriate channels and within 10 working days to Merck Global Safety and Incyte Global Safety if it causes the subject to be excluded from the study, 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 the final dose, any SAE or follow-up to a SAE, including death due to any cause other than progression of the cancer under study, whether or not related to the study products, must be reported to the FDA as appropriate and within 10 working days to Merck Global Safety and Incyte team.

Additionally, any SAE, considered by an investigator to be related to Merck product at any time after signing 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 Merck Global Safety.

Incyte Serious Adverse Event specifics for reporting:

1. Initial Serious Adverse events (SAEs) and/or subsequent follow-up reports should be reported via email to: ***IncytePhVOpsIST@incyte.com***. SAE reports should be for a single subject with any additional documents (i.e. discharge summary, relevant test results) included for the same subject as individual attachments to the email. One email can have multiple attachments as long as each attachment contains relevant information for the same subject.

2. Please email your SAE form with a cover sheet and any additional attachments to the IST email address: ***IncytePhVOpsIST@incyte.com.***

3. Telerx C3i is the PhV Clinical Research Organization (CRO) for Incyte. They will be contacting you for SAE follow-up requests and data clarifications by sending you a data clarification form (DCF). See follow-up section for details on this process. The following is general contact information for Telerx C3i.

TELERX C3I (Incyte PhV CRO)
US SAE fax number 1-866-726-9234

- **Initial reports**

Incyte needs to be notified within 24 hrs of learning of an event as well as providing a completed SAE form emailed to *IncytePhVOpsIST@incyte.com.*

1. SAE reporting for each subject begins the day patient start treatment and up to 30 days after subject has completed or discontinued from the study or until new anti-cancer treatment is initiated, whichever occurs first.

2. All SAE notices are sent from the site to Incyte via a central email address: ***IncytePhVOpsIST@incyte.com*** established for IST sites for this process.

3. SAEs, occurring using Incyte Study drug, are reported in accordance with the effective protocol. SAEs occurring with any another commercial drug are reported to manufacturer of that drug in accordance with regulations and protocol.

4. SAEs related to concomitant medications/drug delivery systems are reported directly to the manufacturers of those drugs/devices in accordance with the package insert. Meaning, follow the SAE manufacturer reporting requirements for all medication other than Epacadostat.

5. All SAE details are recorded on the SAE Report form, regardless of causality to the investigational product and sent via email in accordance with the protocol. If a non-serious Adverse Event (AE) becomes serious, the process for SAE reporting is followed.

6. Additional information requested upon internal Incyte review will be asked by Telerx C3i in the form of a Data Clarification Form (DCF).

- **Follow-up reports**

1. Follow-up SAE reports are sent via email to ***IncytePhVOpsIST@incyte.com*** from the Investigator site.

2. Telerx C3i tracks any critical outstanding follow-up items and questions and contacts the investigational site via a faxed DCF for the additional requested information until all outstanding queries are resolved. A sample of this form is included in Appendix III. This includes requests for hospital discharge summaries, autopsy reports, and death certificates (if applicable), results of relevant laboratory, and diagnostic tests. The investigational site faxes the additional information to Telerx C3i, using the Telerx C3i SAE fax number. The site personnel will update all relevant data on the appropriate SAE Report Form or equivalent to include any new or changed information. The Incyte Safety Representative (IC SR) will monitor outstanding queries and take appropriate action needed for resolution.
3. Any serious SAE upgraded to death or life-threatening requires that the follow up report be emailed to: ***IncytePhVOpsIST@incyte.com*** email address within 24 hours.

- **Regulatory Reporting**

The Investigator Sponsor (George A. Fisher, Jr., MD, PhD) of the IST trial is responsible for meeting expedited reporting requirements to Health Authorities and all participating investigators under their institution's IND. Incyte is responsible for meeting expedited reporting requirements to Health Authorities (HAs) in their respective territory and for cross reporting any Serious Unexpected Suspected Adverse Reaction (SUSAR) originating from IST sponsored studies to Incyte's IND, NDA, and Incyte investigators from Incyte sponsored trials as required.

- **Reporting of Pregnancy**

An "Initial Pregnancy Report" or equivalent must be completed in full and emailed to *IncytePhVOpsIST@incyte.com* within 24 hrs of discovery of a pregnancy of a subject who has taken the Incyte product or the pregnancy of a partner for a subject who has taken the Incyte product. The "Follow-up Pregnancy Report Form" or equivalent must be completed and emailed to *IncytePhVOpsIST@incyte.com* within 30 days after delivery, so that Incyte is provided with information regarding the outcome of the pregnancy. If the pregnancy results in any events which meet the serious criteria (i.e., miscarriage or termination), the SAE reporting process needs to be followed and the timelines associated with an SAE should be followed.

All subjects with SAEs must be followed up for outcome.

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally, investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215 993-1220) and Incyte (*IncytePhVOpsIST@incyte.com*) at the time of submission to FDA.

7.5.2. Events of Clinical Interest (ECIs)

Selected non-serious and SAEs are also known as ECIs, must be reported within 10 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220).

For the time period after the consent has been signed through 30 days following the safety follow-up, any ECI, or follow up to an ECI, whether or not related to study products, must be reported within 10 working days to Merck Global Safety.

ECIs for this study include:

1. An overdose of drug;
2. An elevated AST or ALT lab value that is ≥ 3 x ULN and an elevated total bilirubin lab value that is ≥ 2 x ULN and, at the same time, an alkaline phosphatase lab value that

is < 2 x ULN, 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.

7.6. **Assignment of Intensity and Relationship to Investigational Product (Causality)**

Causal relationship to investigational product as determined by the investigator(s) should be defined based on the definitions below:

- **Related:** There is a reasonable causal relationship to investigational product administration and the adverse event.
- **Not Related:** There is not a reasonable causal relationship to investigational product administration and the adverse event.

The expression "reasonable causal relationship" is meant to convey in general that there are facts (e.g., evidence such as de-challenge/re-challenge) or other arguments to suggest a positive causal relationship.

7.7. **Responsibility for Reporting AEs to Regulatory Authorities**

All AEs will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

7.8. **Evaluating Adverse Events**

All investigators who are qualified physicians and delegated, can evaluate for AEs. All AEs will be graded based on the NCI CTCAE v.5. Any AE which changes in grade over the course of a given episode will have each change of grade recorded independently in the appropriate eCRF. All adverse events regardless of grade must be evaluated for seriousness and causality to the investigational agents. See Table 6 for further guidance on evaluating an AE by grade, seriousness, and causality.

Table 6:Evaluating Adverse Events

An investigator who is a qualified physician, will evaluate all AEs for the following:

V4.03	**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**
Seriousness	A SAE is any AE occurring at any dose or during any use of an investigational drug 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 AE 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 SAE. A pre-existing condition is a clinical condition that is diagnosed prior to the use of the agent 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 Merck and Incyte within 2 working days to meet certain local requirements); or	
	Is an overdose (whether accidental or intentional). Any AE associated with an overdose is considered a SAE for collection purposes. An overdose that is not associated with an AE is considered a non-serious ECI and must be reported within 24 hours to Merck and Incyte.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a SAE 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 AE. If less than 1 day, indicate the appropriate length of time.	
Action taken	Did the AE cause drug to be discontinued?	
Relationship to Study Drug	Did study drug cause the AE? The determination of the likelihood that the investigational agent caused the AE 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 AE based upon the available information. **The following components are to be used to assess the relationship between the investigational agents and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely product caused the AE:	
	Exposure	Is there evidence that the subject was actually exposed to the investigational drug 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 drug? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal drug)?
	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?
	The following components are to be used to assess the relationship between the test drug and the AE: (continued)	
	Dechallenge	Was drug 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 product; or (3) the study is a single-dose drug study); or (4) drug(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to drug on 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 study is a single-dose drug study); or (3) product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY DRUG, OR IF REEXPOSURE TO DRUG POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE MERCK AND INCYTE AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with StudyTreatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding drug or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the CRFs 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 product relationship).**
Yes, there is a reasonable possibility of product relationship.		There is evidence of exposure to drug. The temporal sequence of the AE onset relative to the administration of drug is reasonable. The AE is more likely explained by drug than by another cause.
No, there is not a reasonable possibility of product relationship		Subject did not receive the investigational drugs OR temporal sequence of the AE onset relative to administration of drug is not reasonable **OR** the AE is more likely explained by another cause than the drug. (Also entered for a subject with overdose without an associated AE.)

7.9. **Laboratory Test Abnormalities Definition and Reporting**

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

A Grade 3 or 4 (severe) AE, as per CTCAE v5, does not automatically indicate an SAE unless it meets the definition of serious, as defined in Section 7.5.1, and/or per the investigator's discretion. A dose interruption or adjustment for the laboratory abnormality may be required and should not contribute to the designation of a laboratory test abnormality as an SAE.

7.10. **Handling of Expedited Safety Reports**

In accordance with local regulations, Merck and Incyte will notify investigators of all SAEs that are suspected (related to the investigational products) and unexpected (i.e., not previously described in the IBs) regarding the drugs under study at other sites in other investigations. In the European Union (EU), an event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Investigator notification of these events will be in the form of an expedited safety report (ESR).

Other important findings which may be reported by the sponsor as an ESR include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (e.g., animal) study, important safety recommendations from a study data monitoring committee, or sponsor decision to end or temporarily halt a clinical study for safety reasons.

Upon receiving an ESR from Merck and/or Incyte, the investigator must review and retain the ESR with the IBs. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and

IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.

In addition, suspected serious adverse reactions (whether expected or unexpected) shall be reported by Merck and Incyte to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

7.11. Warnings and Precautions

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

7.12. Data Safety Monitoring Committee

There will be no formal external data monitoring committee for this open-label study. This study will be monitored per standard Stanford's data and safety monitoring schedule.

8. CORRELATIVE/SPECIAL STUDIES

Blood and tissue will be collected during the context of the study for future correlative studies including organoids (tissue) and immune markers (blood). Section 9 outlines the frequency of the testing being done and then being stored with the intent to analyze in the future.

For the context of this particular protocol, we will only be collecting and storing blood, serum, plasma, and tissue that could be used for the indicated testing in the future.

8.1. **Blood Samples**

8.1.1. **Required Research Samples**

Blood will be collected in green and purple top tubes. One 10 mL purple top EDTA tube for whole blood collection and three 10 mL green top tubes for plasma will be collected every 3 weeks prior to pembrolizumab infusion for storage for future research. All these samples will be processed and stored frozen at -80°C.

8.2. **Tissue Samples**

Pre-treatment and on-treatment biopsies are to be collected on patients when safe and feasible.

Details and methods for obtaining, processing, and shipping the fresh tumor biopsy are as follows:

- 6-15 (average 10) core biopsies measuring at least 4mm, if possible 10mm will be obtained from an accessible and safe primary or metastatic tumor site
- When feasible, all core samples should be obtained from the same lesion/location at the appropriate time point
- When feasible, 16-18 gauge needles should be used to obtain core samples. FNA samples are acceptable
- Samples should contain at minimum 20% tumor viability as measured by adequate number of living cells based on H&E slide
- Specimens will be collected/stored in FFPE or as a single cell suspension via the Correlatives Sciences Unit SOP.

9. STUDY CALENDARS

Schedule of Events

	Screening	Treatment Phase[1]				EOT	Post-Treatment	
		C1D1	C2D1	C3D1	Day 1 All Subsequent Cycles	Discontinuation Visit	Follow-Up Visits	Survival Follow-Up
Evaluation/Window	**Day -28 to Day -1**	**Day 1**	**± 3 Days**	**± 3 Days**	**± 3 Days**	**+ 5 Days**	**Every 9 Weeks After Discontinuation (± 7 Days)**	**Every 12 Weeks (± 7 Days)**
ADMINISTRATIVE PROCEDURES								
Informed consent	X							
Inclusion/exclusion criteria	X	X						
Prior medical and cancer history	X							
Concomitant medications review	X	X	X	X	X	X		
Administer Pembrolizumab[2]		X	X	X	X			
Administer Epacadostat[3]		X	X	X	X			
Survival follow-up								X
CLINICAL PROCEDURES AND ASSESSMENTS								
Comprehensive physical exam	X					X		
Targeted physical exam		X	X	X	X		X	
ECOG performance status	X	X	X	X	X	X	X	

1 Treatment cycles are every 3 weeks (~ 21 days ± 3 days).
2 Fixed dose at 200 mg per IV every 3 weeks.
3 Fixed dose at 300 mg orally twice daily every day, all 21 days of each cycle.

		Treatment Phase[1]				EOT	Post-Treatment	
	Screening	C1D1	C2D1	C3D1	Day 1 All Subsequent Cycles	Discontinuation Visit	Follow-Up Visits	Survival Follow-Up
Evaluation/Window	**Day -28 to Day -1**	**Day 1**	**± 3 Days**	**± 3 Days**	**± 3 Days**	**+ 5 Days**	**Every 9 Weeks After Discontinuation (± 7 Days)**	**Every 12 Weeks (± 7 Days)**
Vital signs and weight	X	X[4]	X	X	X	X	X	
12-lead ECG	X					X		
AE assessment		X	X	X	X	X	X	X
EFFICACY MEASUREMENTS								
Radiologic tumor assessment	X[5]				X[6,7]	X[8,9]	X[6]	
LABORATORY ASSESSMENTS[10,11,12]								
Comprehensive serum chemistry	X	X	X	X	X	X	X	
Tumor molecular profiling[13]	X							

4 Height only required to be collected at Cycle 1 Day 1.
5 Initial tumor imaging will be performed within 28 days before the first dose of study treatment. A CT chest/abdomen/pelvis with IV contrast is preferred. MRI abdomen with gadolinium is acceptable for patients with contrast allergies.
6 Imaging on-study will be performed every 9 weeks (± 5 days) after the first dose of study treatment for the first 18 months then every 12 weeks thereafter. On-study imaging should follow calendar days and not be adjusted for delays in cycle starts or extension of treatment cycles due to toxicity. The same imaging technique should be used in a subject throughout the study.
7 Per the RECIST v1.1 and irRC, if imaging shows progressive disease, the imaging assessment should be performed at a minimum of 4 weeks later to confirm progression as described.
8 For patients that discontinue treatment for reasons other than disease progression, every effort should be made to continue monitoring their disease status by radiographic imaging at the imaging interval that was used at the time they came off study until 1) start of new anti-cancer therapy, 2) documented disease progression, 3) death, or 4) end of study, whichever occurs first.
9 If a prior scan was obtained within 4 weeks before the date of discontinuation, then a scan at the discontinuation visit is not required. In subjects who discontinue study drug without confirmed disease progression, a radiological evaluation should be repeated at the time of treatment discontinuation (i.e., date of discontinuation ± 4 week window).
10 If labs at screening are collected within 7 days of Cycle 1 Day 1, these do not need to be repeated at this visit.
11 Pre-dose laboratory results need to be within 2 days of dosing at all cycles.
12 See Table 2 for complete listing of all required laboratory tests required.

	Screening	Treatment Phase[1]				EOT	Post-Treatment	
		C1D1	C2D1	C3D1	Day 1 All Subsequent Cycles	Discontinuation Visit	Follow-Up Visits	Survival Follow-Up
Evaluation/Window	**Day -28 to Day -1**	**Day 1**	**± 3 Days**	**± 3 Days**	**± 3 Days**	**+ 5 Days**	**Every 9 Weeks After Discontinuation (± 7 Days)**	**Every 12 Weeks (± 7 Days)**
Hematology with differential	X	X	X	X	X	X	X	
Lipid panel	X	X	X	X	X	X		
Coagulation panel (PT, aPTT, INR[14]	X							
Endocrine function testing[15]	X	X	X	X	X		X	
Serum pregnancy test or urine[16]	X							
Tumor Markers[17]		X	X	X	X	X		
Urinalysis	X	X	X	X	X	X		
Required research samples (blood)		X[18]	X	X	X			
TUMOR BIOPSY/ARCHIVAL TISSUE COLLECTION								
Fresh tissue collection for Correlative studies (tissue) [19]	X			X				

13 Tumor molecular profilingcan be performed on archived tissue or newly obtained during the study participation
14 If a coumadin-based anticoagulant is given, INR should be monitored weekly for the first 4 weeks after initiation of therapy and again upon discontinuing epacadostat.
15 TSH required at all day 1 visits, T3 and fT4 only required if TSH is abnormal or patient is symptomatic.
16 For women of childbearing potential, a serum pregnancy test is required at screening but must be within 3 days before first dose of study treatment. Pregnancy tests (serum or urine) should be repeated as needed if required by institutional regulations.
17 CEA and CA19-9 will be checked at baseline on C1D1 prior to Pembrolizumab and Epacadostat and, if elevated, followed every 9 weeks during therapy.
18 Before pembrolizumab dose every 3 weeks
19 Fresh tumor biopsy will be collected pre-treatment (between day -14 to day 0) and on treatment (day 42 ± 5 days). For additional reference go to section 4.9.3 and 8.2

Schedule of Events – Second Course Phase/Retreatment[20]

		Treatment Phase[21]				EOT	Post-Treatment	
	Progression	C1D1	C2D1	C3D1	Day 1 All Subsequent Cycles	Discontinuation Visit	Follow-Up Visits	Survival Follow-Up
Evaluation/Window	**Day -14 to Day -1**	**Day 1**	**± 3 Days**	**± 3 Days**	**± 3 Days**	**+ 5 Days**	**Every 9 Weeks After Discontinuation (± 7 Days)**	**Every 12 Weeks (± 7 Days)**
ADMINISTRATIVE PROCEDURES								
Re-check inclusion/exclusion criteria[22]	X	X						
Updated medical and cancer history	X							
Concomitant medications review	X	X	X	X	X	X		
Administer Pembrolizumab[23]		X	X	X	X			
Administer Epacadostat[24]		X	X	X	X			
Survival follow-up								X
CLINICAL PROCEDURES AND ASSESSMENTS								
Comprehensive physical exam	X					X		
Targeted physical exam		X	X	X	X			
ECOG performance status	X	X	X	X	X	X		

20 Fresh tissue collection not required during the second course phase.
21 Treatment given every 3 weeks (~ 21 days ± 3 days).
22 Patient must meet required re-start criteria as defined in Section 4.8.
23 Fixed dose at 200 mg per IV every 3 weeks.
24 Fixed dose, resume with the same dose level of first course, orally twice daily every day, all 21 days of each cycle.

		Treatment Phase[21]				EOT	Post-Treatment	
	Progression	C1D1	C2D1	C3D1	Day 1 All Subsequent Cycles	Discontinuation Visit	Follow-Up Visits	Survival Follow-Up
Evaluation/Window	**Day -14 to Day -1**	**Day 1**	**± 3 Days**	**± 3 Days**	**± 3 Days**	**+ 5 Days**	**Every 9 Weeks After Discontinuation (± 7 Days)**	**Every 12 Weeks (± 7 Days)**
Vital signs and weight	X	X[25]	X	X	X	X		
12-lead ECG						X		
AE assessment	X[26]	X	X	X	X	X	X	X
EFFICACY MEASUREMENTS								
Radiologic tumor assessment	X[27]				X[28,29]	X	X	
LABORATORY ASSESSMENTS								
Comprehensive serum chemistry	X	X	X	X	X	X	X	
Hematology with differential	X	X	X	X	X	X	X	
Lipid panel	X	X	X	X	X	X		
Coagulation panel (PT, aPTT, INR)	X							
Endocrine function testing	X	X	X	X	X		X	

25 Height required to be collected at Cycle 1 Day 1 only.
26 All AEs from previous treatment with pembrolizumab and epacadostat must be ≤ grade 1 and stable.
27 For subjects that have had a scan within 14 days of restarting therapy due to progression, scan does not need to be repeated pre-dosing.
28 Imaging in the second course phase will be performed every 9 weeks (± 5 days) after the first dose of study treatment for the first 18 months then every 12 weeks thereafter. On-study imaging should follow calendar days and not be adjusted for delays in cycle starts or extension of treatment cycles due to toxicity. The same imaging technique should be used in a subject throughout the study.
29 Per the RECIST v1.1 and irRC, if imaging shows progressive disease, the imaging assessment should be performed at a minimum of 4 weeks later to confirm progression as described.

		Treatment Phase[21]				EOT	Post-Treatment	
	Progression	C1D1	C2D1	C3D1	Day 1 All Subsequent Cycles	Discontinuation Visit	Follow-Up Visits	Survival Follow-Up
Evaluation/Window	**Day -14 to Day -1**	**Day 1**	**± 3 Days**	**± 3 Days**	**± 3 Days**	**+ 5 Days**	**Every 9 Weeks After Discontinuation (± 7 Days)**	**Every 12 Weeks (± 7 Days)**
Serum pregnancy test or urine	X[30]							
Tumor Markers	X	X	X	X	X	X		
Urinalysis	X	X	X	X	X	X		
Required research samples		X[31]	X	X	X			

30 For women of childbearing potential, a pregnancy test must be done within 3 days of dosing on the second course phase.
32 Before pembrolizumab dose every 3 weeks

10. MEASUREMENTS

10.1. Tumor Imaging Evaluations

Imaging of the chest, abdomen and pelvis is required at screening/baseline, every 9 weeks (± 5 days) for the first 18 months, then every 12 weeks thereafter regardless of the location of known metastases. Similar methods of tumor assessment and similar techniques must be used to characterize each identified and reported lesion at screening/baseline and during subsequent tumor assessments. Imaging-based evaluation is preferred to clinical examination. All measurements should be taken and recorded in metric notation using a ruler or calipers.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans), but NOT for the chest.

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

10.2. Definition of Measurable/Non-Measurable or Index/Non-Index Lesions

10.2.1. Measurable and Non-Measurable Lesions

Measurable lesions are lesions that can be accurately measured in two perpendicular diameters, with at least one diameter ≥ 10 mm and the other dimension ≥ 10 mm (10 mm x 10 mm for spiral CT). The area will be defined as the product of the largest diameter with its perpendicular. Skin lesions can be considered measurable.

Non-measurable (evaluable) lesions are all other lesions, including unidimensionally measurable disease and small lesions (lesions without at least one diameter ≥ 20 mm), and any of the following:

- Lesions occurring in a previously irradiated area (unless they are documented as new lesions since the completion of radiation therapy), bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusion, lymphangitis cutis/pulmonitis, abdominal masses

that are not pathologically/cytologically confirmed and followed by imaging techniques and cystic lesions.

All measurable and non-measurable lesions should be measured at screening/baseline and at the defined tumor assessment time points (~ every 9 weeks ± 5 days for the first 18 months then every 12 weeks thereafter). Extra assessments may be performed, as clinically indicated, if there is a suspicion of progression.

10.2.2. Index and Non-Index Lesions

All measurable lesions, up to a maximum of five lesions per organ and ten lesions in total, should be identified as index lesions to be measured and recorded in the medical record at Screening. The index lesions should be representative of all involved organs. In addition, index lesions should be selected based on their size (lesions with the longest diameters), their suitability for accurate repeat assessment by imaging techniques, and how representative they are of the patient's tumor burden. At screening, a sum of the products of diameters (SPD) for all index lesions will be calculated and considered the baseline sum of the products of diameters. Response criteria to be followed are listed below. The baseline sum will be used as the reference point to determine the objective tumor response of the index lesions at tumor assessment.

Measurable lesions, other than index lesions, and all sites of non-measurable disease, will be identified as non-index lesions. Non-index lesions will be recorded in the medical record and should be evaluated at the same assessment time points as the index lesions. In subsequent assessments, non-index lesions will be recorded as "stable or decreased disease," "absent," or "progression."

10.2.3. Evaluation of Target Lesions

Complete Response: Complete disappearance of all target lesions.

Partial Response: Decrease, relative to baseline, of 30% or greater in the sum of the diameters of the two largest perpendicular diameters.

Stable Disease: Does not meet criteria for complete or partial response, in the absence of progressive disease. Subject with PR or CR that is not confirmed after at least 6 weeks are scored as SD unless they have new primary lesions.

Progressive Disease: At least 20% increase in the sum of the products of all target lesions (taking as reference the smallest sum recorded at or following baseline) and/or the appearance of any new lesion(s). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

10.2.4. Evaluation of Non-Target Lesions

Complete Response: Complete disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm in short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease: Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions.

10.3. Assessment of Disease According to RECIST v1.1 and irRC for Solid Tumors

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

- Absence of signs and symptoms indicating disease progression
- No decline in ECOG performance status
- Absence of rapid progression of disease

Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

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

Table 7: Imaging and Treatment after First Radiographic Evidence of Progression

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

Note: If a subject with confirmed radiographic progression (i.e., 2 scans at least 28 days apart demonstrating progressive disease) is clinically stable or clinically improved, and there is no further increase in the tumor dimensions at the confirmatory scan, an exception may be considered to continue treatment if in the best interest of the patient clinically. Meaning, the investigator can continue if the risk-benefit is acceptable to continue the patient on study. Clinically stable subjects should also have at the confirmatory scan no further increase in the

target lesions, no unequivocal increase in non-target lesions, and no additional new lesions develop (non-worsening PD) to continue study treatment.

Imaging during the follow-up period is to be repeated every 9 weeks (63 ± 5 days) for subjects who discontinue study treatment for reasons other than disease progression until the subject experiences confirmed disease progression or starts a new antineoplastic therapy.

10.4. Response Endpoints

Pembrolizumab and epacadostat are expected to trigger immune-mediated responses, which require activation of the immune system prior to the observation of clinical response. Such immune activation may take weeks to months to be evident.

Table 8: Response Evaluations based on Endpoints

	Progression Free Survival (PFS)	**Response Rate (RR)**	**Overall Survival (OS)**	**Safety**
Primary or Secondary	*Primary*	*Secondary*	*Secondary*	*Secondary*
Definition and Time Frame	Time from first treatment to documented disease progression or death due to any cause	Defined as proportion of patients with RECIST v1.1 response (sum of partial and complete responses).	Time from first treatment until the day of death due to any cause	Assessed on the basis of adverse events (AEs; graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03)
Safety Issue (Yes/No)	No	No	No	**Yes**
Relevant Subset	Patients who receive baseline imaging and at least first follow-up imaging at 9 weeks.	Patients who receive baseline imaging and at least first follow-up imaging at 9 weeks.	All enrolled patients	Patients who receive at least 1 dose of pembrolizumab.
Measurement Method	CT or MRI every 9 weeks	CT or MRI every 9 weeks	CT or MRI every 9 weeks	CTCAE v5
Measurement Time Points	Every 9 weeks	Every 9 weeks	Every 9 weeks	Day 1 of each cycle

11. REGULATORY CONSIDERATIONS

11.1. Institutional Review of Protocol

The protocol, the proposed informed consent and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the

Stanford IRB and Stanford Cancer Institute Scientific Review Committee (SRC). Any changes made to the protocol will be submitted as a modification and will be approved by the IRB prior to implementation. The Protocol Director will disseminate the protocol amendment information to all participating investigators.

11.2. Data and Safety Monitoring Plan

The Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) will be the monitoring entity for this study. The DSMC will audit study-related activities to determine whether the study has been conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). This may include review of the following types of documents participating in the study: regulatory binders, case report forms, eligibility checklists, and source documents. In addition, the DSMC will regularly review serious adverse events and protocol deviations associated with the research to ensure the protection of human subjects. Results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as needed.

11.3. Data Management Plan

The Protocol Director, or his/her designee, will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific CRFs will document treatment outcomes for data analysis. CRFs will be developed using the OnCore database system and will be maintained by the study team. CRFs will be electronic and only accessible to the research team via password, dual-authentication database. All research charts will be kept in a locked office.

11.4. Study Monitoring

The study will be monitored by Stanford's internal Data Safety Monitoring Committee (DSMC) on an annual basis per institutional guidelines.

11.5. Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles

underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive IRB/IEC approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to Genentech immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective task(s). This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure, debarment).

Systems with procedures that ensure the quality of every aspect of the study will be implemented.

11.6. Protocol Adherence

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

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

subject or validity of the investigation. The investigator must send a copy of the approval letter from the IRB to the sponsor or its designee and retain the original in the site study regulatory file.

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

11.7. Financial Disclosure

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

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

11.8. Compliance with Study 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 study is solely responsible for determining whether the study and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Information posted

will allow subjects to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study site contact information.

11.9. Quality Control And Quality Assurance

11.9.1. Pharmaceutical Company Audits

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

11.9.2. Inspection by Regulatory Authorities

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

11.10. Ethics

11.10.1. Ethical Conduct of the Study

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

11.10.2. Ethics Review

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

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

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

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

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

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

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

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

11.11. Data Privacy

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

11.12. Data Handling and Record Keeping

11.12.1. Inspection of Records

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

11.12.2. Retention of Records

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

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

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

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

11.13. Confidentiality

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

12. STATISTICS CONSIDERATIONS

12.1. Statistical Design

This is a single-stage study for the doublet epacadostat and pembrolizumab. A 6-month PFS of 20% was observed using single agent pembrolizumab and is the basis for the null hypothesis of the present study (Bang, abstract 4001, GI ASCO 2015). We will enroll 30 patients over 18 months and follow patients for at least 6 months. This design has 80% power to reject a 20% PFS rate, if the true PFS is 39%. Calculation based on binomial probabilities with a one-sided significance of 10%. The level of significance for the primary endpoint in Phase 2 is one-sided 10%, which is deemed acceptable for a proof-of-concept study.

12.2. Safety Analyses

12.2.1. Analysis Plan

The analysis will be done on the intent to treat population and patients who drop out will be censored at the point of last follow up.

The primary endpoint of the study is 6-month Progression-free survival (PFS), which is defined as number of days from the first day of taking study dose to the earlier of death or disease progression by RECIST v1.1 for solid tumors. Median PFS will be estimated using the Kaplan-Meier method.

12.3. Secondary Analyses

Secondary efficacy analysis will be conducted for the efficacy evaluable population. Secondary endpoints and analyses are as follows:

To evaluate response rate (RR). Response will be determined by RECIST v1.1 for solid tumors. The 95% exact CI for the RR will be estimated using the Clopper-Pearson method. For objective responders, the duration of response is the time from the first objective response contributing to an objective response, to the first objective response of PD (by RECIST v1.1) occurring after the first objective response contributing to the objective response.

To evaluate overall survival (OS). Time-to-event data will be analyzed by the Kaplan-Meier method, treating subjects with no observed death or progression as censored at their last date known to be alive. For the OS analysis, the nonparametric Kaplan-Meier method will be used to estimate the survival time distribution and the median survival.

To assess the safety and tolerability of epacadostat in combination with pembrolizumab. AEs will be coded by the MedDRA, and incidences will be tabulated by preferred term and system organ class for all events, related events, and events ≥ Grade 3. Severity of AEs will be based on the CTCAE v5 scale as indicated. Quantitative safety variables and their changes from baseline (laboratory, vital signs) will be summarized with descriptive statistics. Clinically significant abnormal values will be flagged and tabulated based on predefined criteria. Exposure will be analyzed by describing dose intensity, which is defined as the dose-received divided by the dose planned over a given time interval. This will be done by cycle as well as overall cycles received for epacadostat and pembrolizumab. For each cycle, incidences of dose reductions and cycle

delays will also be tabulated, by reason for the reduction or delay. The percentage of subjects with any delay and/or reduction will also be calculated.

Clinical Laboratory Tests. The clinical laboratory data will be analyzed using summary statistics (e.g., means and frequencies), and no formal statistical comparisons among the treatments are planned. In addition, distributions of key laboratory parameters (including hemoglobin, neutrophils, and platelets) will be plotted over time; these values will also be classified into CTCAE toxicity grades and tabulated. Descriptive statistics and mean change from baseline will be determined for vital signs at each assessment time. Vital sign results will be reviewed for clinically notable abnormalities.

12.4. Sample Size

We will enroll 30 patients over 18 months and follow patients for at least 6 months.

12.5. Criteria for Future Studies

If the sample size is justified by precision only, state the outcomes that constitute success. If the protocol is part of a sequence of studies, state the statistical criteria that will be applied. If this is a pilot study, state what result would convince you to begin a fully powered study.

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14. APPENDICES

14.1. **APPENDIX A:** PARTICIPANT ELIGIBILITY CHECKLIST

Protocol Title:	Phase II Study Of Epacadostat (INCB024360) With Pembrolizumab (MK-3475) In Metastatic Or Unresectable Gastroesophageal Junction And Gastric Adenocarcinoma Requiring Paired Biopsies
Protocol Number:	IRB-40823 / GI0015
Principal Investigator:	George A. Fisher, Jr., MD, PhD

I. Subject Information:

Subject Name/ID:
Gender: ☐ Male ☐ Female

II. Inclusion/Exclusion Criteria

	Yes	No	Supporting Documentation*
Inclusion Criteria			
1. Age ≥ 18 years of age on day of signing informed consent	☐	☐	
2. Be willing and able to provide written informed consent for the study	☐	☐	
3. Histologically or cytologically confirmed adenocarcinoma of the distal esophagus, gastroesophageal junction or stomach, including patients with HER2+ disease • Distal esophagus is defined as within 5 cm of the GEJ	☐	☐	
4. Patients must have metastatic or unresectable disease, including those with HER2+ disease	☐	☐	
5. Must have progressed on at least one line of prior therapy for metastatic disease, or be intolerant to that therapy if they have not progressed; for HER2+ disease patients should have received prior trastuzumab	☐	☐	

6. Life expectancy of ≥ 12 weeks	☐	☐	
7. Have a performance status of 0 or 1 (ECOG)	☐	☐	
8. Have measurable disease per RECIST v1.1 assessed within 4 weeks prior to study entry	☐	☐	
9. Tumor deemed amenable to biopsy by core for metastatic site or endoscopic biopsy for primary tumor (for both before and on-treatment biopsies)	☐	☐	
10. Patient must be willing to undergo 2 biopsies – before and on-treatment, provided the procedure is not deemed high-risk and is clinically feasible.	☐	☐	
11. Demonstrate adequate organ function within 7 days before treatment initiation, as defined below: • Absolute neutrophil count ≥ 1500 /mcL • Platelets ≥ 100,000 /mcL • Hemoglobin ≥ 9 g/dL **or** ≥ 5.6 mmol/L without transfusion or EPO dependency (within 7 days of assessment) • Serum creatinine ≤ 1.5 x ULN **or** measured creatinine clearance ≥ 60 mL/min (*for subjects that have creatinine levels > 1.5 x ULN)* • Total bilirubin ≤ 1.5 x ULN **or** direct bilirubin ≤ ULN • AST and ALT ≤ 2.5 x ULN (*for subjects that have liver metastases, ≤ 5 x ULN)* • Albumin ≥ 2.5 mg/dL • INR or PT ≤ 1.5 x ULN (*if subjects are on anticoagulation therapy, PT/INR must be within therapeutic range)* • aPTT ≤ 1.5 x ULN (*if subjects are on anticoagulation therapy, PT/INR must be within therapeutic range)*	☐	☐	
12. Female subject of childbearing potential should have a negative urine or serum pregnancy within 3 days prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed negative, a serum pregnancy test will be required	☐	☐	
13. Female subjects of childbearing potential must be willing to use an adequate method of contraception	☐	☐	

starting with the date of consent through 120 days after the last dose of study medication			
14. Male subjects of childbearing potential must agree to use an adequate method of contraception starting with the date of consent through 120 days after the last dose of study medication	☐	☐	
15. Must be able to swallow pills	☐	☐	
Exclusion Criteria			
1. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first planned dose of treatment	☐	☐	
2. Has known hypersensitivity to pembrolizumab and/or epacadostat or any of their excipients	☐	☐	
3. Has had a prior anti-cancer monocloncal antibody within 4 weeks prior to day 1 or who has not recovered (i.e., ≤ grade 1 or to baseline) from AEs due to agents administered more than 4 weeks earlier. • Denosumab for treatment for bone metastases is allowed	☐	☐	
4. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study day 1 or who has not recovered (i.e., ≤ grade 1 or to baseline) from AEs due to previously administered agents • Subjects with ≤ grade 2 neuropathy are an exception to this criterion and may qualify for the study • If subjects have received major surgery, they must have recovered adequately from surgery prior to starting therapy	☐	☐	
5. Patients who have been treated on any Merck-sponsored pembrolizumab containing gastric cancer pivotal trial will require prior authorization by Merck in order to enroll in this study	☐	☐	
6. Prior therapy with IDO-inhibitors	☐	☐	
7. Has active autoimmune disease that has required	☐	☐	

systemic treatment in the past 2 years (i.e., with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). • Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency etc.) is not considered a form of systemic treatment			
8. Has known history of, or any evidence of active, non-infectious pneumonitis	☐	☐	
9. Has received a live vaccine within 30 days of planned start of therapy • Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are **NOT** allowed	☐	☐	
10. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis • Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least 4 weeks prior to the first dose of study treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to study treatment • Carcinomatous meningitis is excluded regardless of clinical stability • Patient with prior CNS metastases treated w/ prior RT will also need: A. 2 months off RT before starting study or 4 weeks following XRT if MRI is stable and the patient is off steroids, B. Baseline MFI with no edema., and C. stable for at least 8 weeks.	☐	☐	
11. Has known additional malignancy that is progressing or requires active treatment • Exceptions include: basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy	☐	☐	

12. Has active infection requiring systemic therapy	☐	☐	
13. Has a known history of active TB (bacillus tuberculosis)	☐	☐	
14. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] detected	☐	☐	
15. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment	☐	☐	
16. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies)	☐	☐	
17. Is pregnant or breastfeeding, or expecting to conceive or father children within projected duration of the study, starting with pre-screening or screening visit through 120 days after the last dose of study treatment	☐	☐	
18. Has had Monoamine oxidase inhibitors within 21 days before screening	☐	☐	
19. Has any history of serotonin syndrome after receiving 1 or more serotonergic drugs	☐	☐	
20. Has presence of a gastrointestinal condition that may affect drug absorption	☐	☐	
21. Use of systemic corticosteroids	☐	☐	
22. Has history or presence of an abnormal ECG which, in the investigator's opinion, is clinically significant. QTcF > 480 ms or presence of a Left Bundle Branch Block (LBBB). If the QRS duration > 120ms, the JTc can be used in place of the QTcF, The JTc must be < 340 ms.	☐	☐	
23. Has history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subjects 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 investigator	☐	☐	
24. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study	☐	☐	
25. Has known allergy or reaction to any component of either study drug or formulation components	☐	☐	

*All subject files must include supporting documentation to confirm subject eligibility. The method of confirmation can include, but is not limited to, laboratory test results, radiology test results, subject self-report, and medical record review.

III. Statement of Eligibility

By signing this form of this study, I verify that this subject is [☐ **eligible** / ☐ **ineligible**] for participation in the study. This study is approved by the Stanford Cancer Institute Scientific Review Committee, the Stanford IRB, and has finalized financial and contractual agreements as required by Stanford School of Medicine's Research Management Group.

Treating Physician Signature:	Date:
Printed Name:	

Secondary Reviewer Signature:	Date:
Printed Name:	

Study Coordinator Signature:	Date:
Printed Name:	

14.2. **APPENDIX B:** INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS

For Subjects Participating in the Study:

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

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

14.3. **APPENDIX C**: 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.	

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

Monoamine Oxidase Inhibitors	**Drugs Associated With Significant Monoamine Oxidase Inhibitory Activity**	**UGT1A9 inhibitor**
Hydrazines (example phenelzine) Isocarboxazid Tranylcypromine Brofaromine Rasagiline Selegiline	Meperidine Linezolid Methylene blue	acitretin, amitriptyline, androsterone, cyclosporine, dasatinib, diclofenac, diflunisal, efavirenz, erlotinib, estradiol (17-beta), flutamide, geftinib, gemfibrozil, glycyrrhetinic acid glycyrrhizin, imatinib, imipramine, ketoconazole, linoleic acid, mefenamic acid, mycophenolic acid, niflumic acid, nilotinib, phenobartital, phenylbutazone, phenytoin, probenecid, propofol, quinidine, ritonavir, Sorafenib, sulfinpyrazone, valproic acid, and verapmil.

14.5. **APPENDIX E**: 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).[5,6] Signs of excess serotonin range from tremor and diarrhea in mild cases to delirium, neuromuscular rigidity, and hyperthermia in life-threatening cases. The difficulty for clinicians is that mild symptoms may be easily overlooked, and an inadvertent increase in the dose of the causative agent or the addition of a drug with proserotonergic effects may provoke a dramatic clinical deterioration.

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

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

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

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

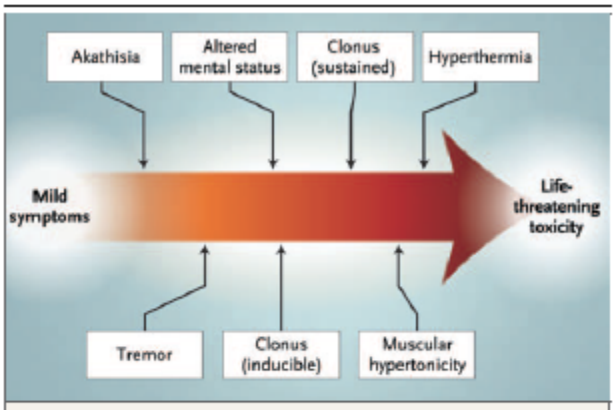

Figure 1. **Spectrum of Clinical Findings.**
Manifestations of the serotonin syndrome range from mild to life-threatening. The vertical arrows suggest the approximate point at which clinical findings initially appear in the spectrum of the disease, but all findings may not be consistently present in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

MANIFESTATIONS

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

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

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

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

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

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

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

PATHOPHYSIOLOGY AND MOLECULAR MECHANISMS

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

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

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

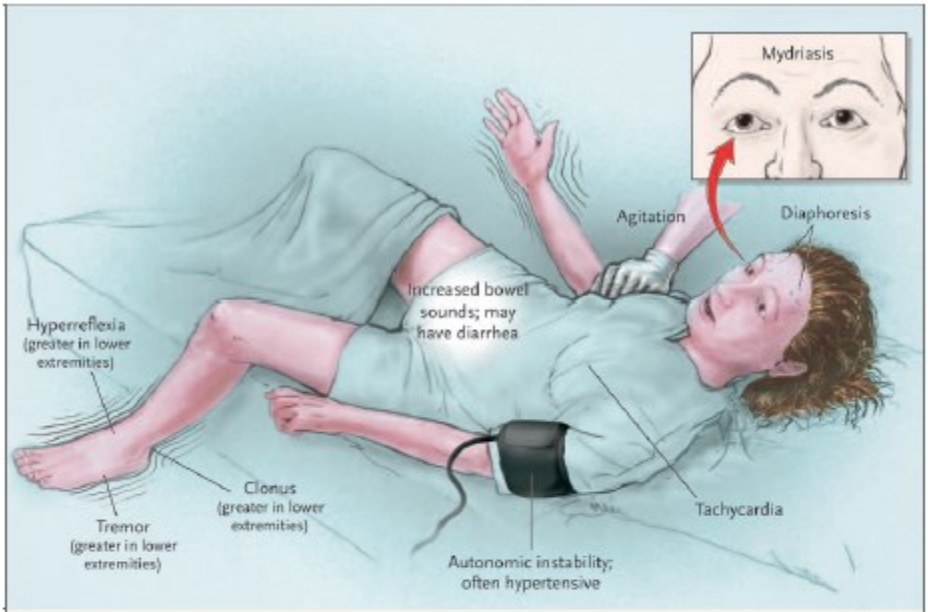

Figure 2. Findings in a Patient with Moderately Severe Serotonin Syndrome.
Hyperkinetic neuromuscular findings of tremor or clonus and hyperreflexia should lead the clinician to consider the diagnosis of the serotonin syndrome.

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

DIAGNOSIS

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

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

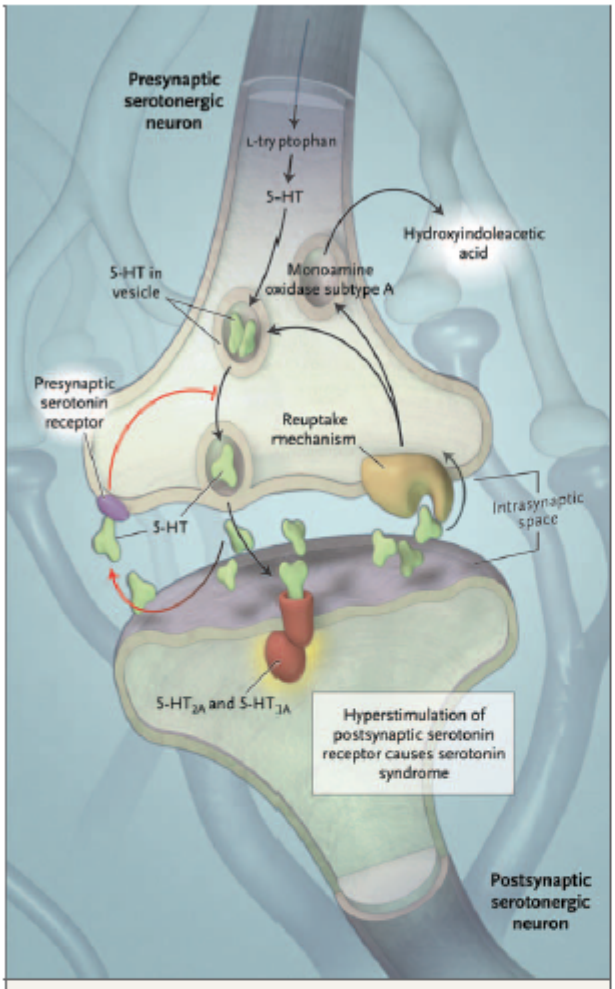

Figure 3. Serotonin Biosynthesis and Metabolism.
Serotonin is produced in presynaptic neurons by hydroxylation and decarboxylation of L-tryptophan. Serotonin is then incorporated into vesicles, where it resides until it is needed for neurotransmission. After axonal stimulation, serotonin is released into the intrasynaptic space; presynaptic serotonin receptors function as a feedback loop to inhibit exocytosis of vesicles (shown in red). Serotonin then binds to postsynaptic receptors to effect neurotransmission. A reuptake mechanism returns serotonin to the cytoplasm of the presynaptic neuron, where it is reintroduced into vesicles. Serotonin is then metabolized by monoamine oxidase subtype A to hydroxyindoleacetic acid.

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

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

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

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

MANAGEMENT

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

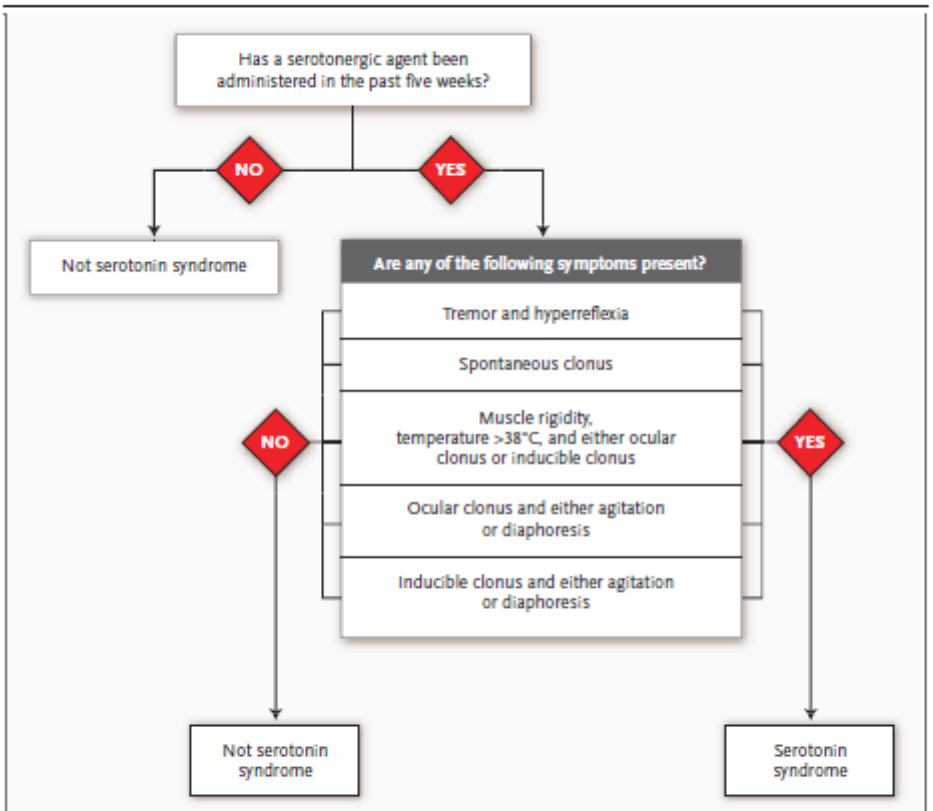

Figure 4. Algorithm for Diagnosis.

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

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

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

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

Pharmacologically directed therapy involves the

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

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

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

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

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

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

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

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

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

PREVENTION

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

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14.6. **APPENDIX F:** ADMINISTRATION OF PEMBROLIZUMAB

Administration of pembrolizumab will be witnessed by the investigator and/or site staff. The total volume of study treatment infused will be compared to the total volume prepared to determine compliance with each dose administered.

On day 1 of every cycle subjects will receive a 200 mg flat dose of pembrolizumab on an every-3-week schedule; this is 2 vials of 100 mg/4mL per infusion. Intrasubject dose escalation of pembrolizumab is not permitted.

Formulation and administration instructions for pembrolizumab are provided below.

- Pembrolizumab infusion solutions should be prepared in 0.9% Sodium Chloride Injection, USP (normal saline) or 5% Dextrose Injection, USP (5% dextrose) and the final concentration of Pembrolizumab in the infusion solutions should be between 1.0 mg/mL and 10.0 mg/mL.
- Pembrolizumab SHOULD NOT BE MIXED WITH OTHER RECONSTITUTION DILUENTS.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Discard the drug product vial if extraneous particulate matter other than translucent to white proteinaceous particles are observed.
- Do not use Pembrolizumab if discoloration is observed.
- DO NOT SHAKE OR FREEZE THE VIAL(S).
- DO NOT ADMINISTER THE PRODUCT AS AN [INTRAVENOUS (IV) PUSH OR BOLUS].
- DO NOT COMBINE, DILUTE OR ADMINISTER THE PRODUCT AS AN INFUSION WITH OTHER MEDICINAL PRODUCTS.

Preparation of Infusion Solution

- Aseptic technique must be strictly observed throughout the preparation procedure preferably in a biologic safety cabinet or hood since no anti-microbial preservative is present in the solutions.

- Equilibrate required number of Pembrolizumab vials to room temperature
- Choose a suitable infusion bag size so that the following conditions are met:
    - Concentration of Pembrolizumab is between 1.0 mg/mL and 10.0 mg/mL
    - The infusion volume to bag capacity ratio should not be less than 0.3. In other words, the bag must be filled to at least 30% of its capacity.
- Choose a suitable infusion bag material. The bag may be empty or it may contain normal saline The following infusion bag materials are compatible with Pembrolizumab:
    - PVC plasticized with DEHP
    - Non-PVC (polyolefin)
    - EVA
    - PE lined polyolefin

    *Contact Sponsor for materials not listed above
- Calculate the volume of Pembrolizumab and normal saline required to prepare the infusion (admixture) bag

    Volume of Pembrolizumab (mL) = required dose amount (mg) / 25.0 (mg/mL)

    Volume of normal saline = total infusion volume – volume of Pembrolizumab from above
- If a bag pre-filled with normal saline is being used, remove the excess volume of normal saline using a sterile syringe (Polypropylene, latex-free) attached to a suitable needle. Keep in consideration the excess bag fill volume as well as the volume of reconstituted Pembrolizumab to be added to the bag to prepare the infusion solution.
- If an empty bag is being used, withdraw the necessary volume of normal saline from another appropriate bag and inject into the empty bag. Keep in consideration the volume of reconstituted Pembrolizumab to be added to the bag to prepare the infusion solution.

- Withdraw the required volume of Pembrolizumab from the vial(s) (up to 4 mL from each vial) using a sterile syringe attached to a suitable needle. The vial(s) may need to be inverted to remove solution.

  Volume of Pembrolizumab (mL) = required dose amount (mg) / 25.0 (mg/mL)

  Note: If it is necessary to use several vials, it is advisable to withdraw from several vials into a suitable size single use syringe using a new needle for each vial.

- Add the required Pembrolizumab into the infusion IV bag containing normal saline and gently invert the bag 10-15 times to mix the solution.

Infusion Instructions

- Pembrolizumab infusions should be administered over a period of 30 minutes, with a window of -5 and +10 minutes, using an infusion pump. A central catheter is not required for infusion; however if a subject has a central venous catheter in place, it is recommended that it be used for the infusion.

  The following infusion set materials are compatible with Pembrolizumab:

  - PVC Infusion set that is plasticized using DEHP
  - PVC and tri-(2-ethylhexyl) trimellitate (TOTM) infusion set
  - Polyethylene lined PVC infusion set
  - PVC Infusion set that is plasticized using Di-2-ethylhexyl Terephthalate (DEHT)
  - Polyurethane set

- A sterile, non-pyrogenic, low-protein binding 0.2 to 5 µm in-line-filter made of polyethersulfone (PES) must be used during administration to remove any adventitious particles. If the infusion set does not contain 0.2 to 5 µm in-line filter, it is recommended to use 0.2 to 5 µm add-on filter which may contain an extension line (Note: the materials of the extension line and filter should be as mentioned above).

- Attach the infusion line to the pump and prime the line, either with normal saline (at least 25 mL) or with infusion solution as per local SOP, before starting the infusion.

- Infuse Pembrolizumab over approximately 30 minutes, with a window of -5 and +10 minutes, through a peripheral line or indwelling catheter.
    - Whenever possible, the lowest infusion rate should be used that will allow completion of the infusion within the 30 minutes
    - Maximum rate of infusion should not exceed 6.7 mL/min. through a peripheral line or indwelling catheter. However, when it is necessary to infuse a larger volume (i.e. 250 mL), the flow rate may go as high as 10 mL/mL (maximum) in order to keep the infusion within the window as defined above.
- Use 30 mL normal saline to flush the infusion line at the end of infusion. If institutional guidelines do not allow the flushing of the infusion line at the completions of the infusion, please prepare excess volume of drug/diluent admixture solution that is required to make up for the volume of the dosing solution lost in the infusion line. For example if a subject is receiving 100 mL IV infusion and it is known that 18mL will be left in the infusion line since the line is not flushed, the pharmacist should prepare 118 mL of drug/diluent admixture solution in a 200 mL bag to make sure that the 100 mL will be delivered to the subject.
- DO NOT CO-ADMINISTER OTHER DRUGS THROUGH THE SAME INFUSION LINE.
- UNUSED INFUSION SOLUTION FOR INJECTION SHOULD NOT BE USED FOR ANOTHER INFUSION OF THE SAME SUBJECT OR DIFFERENT SUBJECT.
- Discard any unused portion left in the vial, as the product contains no preservative.

14.7. APPENDIX G: TEMPERATURE AND LIGHT EXCURSION FORM FOR EPACADOSTAT

Temperature Excursion Report Form

After completion, email this page together with the Site Temperature Log or TempTale downloaded data immediately to the tempex@incyte.com mailbox and copy the following Sponsor contacts: Jennifer Kelley (jkelley@incyte.com), Jennifer Davis (jdavis@incyte.com) and Mark Goetz (mgoetz@incyte.com)

Incyte PAREXEL

1. To be filled out by **INVESTIGATIONAL CENTER STAFF:**

In the event of temperature excursion during storage of study drug at your investigational center, please complete all fields

INCB024360 bottles: Store at room temperature (15-30°C)

MK-3475 vials: Store between 2-8 Degrees Celsius (Reconstituted if not used immediately should be stored between 2-8 Degrees Celsius up to 20 hours and allowed to equilibrate to room temperature prior to subsequent use. MK-3475 solutions may be stored at room temperature for a cumulative time of up to 4 hours. This includes room temperature storage of reconstituted or liquid MK-3475 solution in vials, room temperature storage of infusion solution in the IV bag and the duration of infusion.

Site number:	
Principal Investigator:	

Affected (Please select one)	Lot-Number	Retest/Expiry date	No. of Container
INCB024360 ☐			
MK-3475 ☐			

Date of temperature excursion / alarm:	
Date excursion / alarm detected:	
Length of excursion (HH:MM):	
Min/Max temperature recorded:	

Please provide information about the cause of the temperature excursion - tick the appropriate box (es):

- ☐ Hot weather (temperature excursion above 30 Degrees Celsius for INCB024360 /above 8 Degrees Celsius for MK-3475)
- ☐ Cold weather (temperature excursion below 15 Degrees Celsius for INCB024360/ and below 2 Degrees Celsius for MK-3475
- ☐ Temperature log misplaced / moved/not monitored
- ☐ Was not protected from light or humidity
- ☐ Other
- ☐ Unknown

Please provide specific detail about the temperature excursion (Please attach copies of temperature monitor logs/graphs, etc. when available):

Site Email address to return response: _____

If no EMAIL available please provide FAX Number: _____

Were any of the affected containers dispensed to or administered to study subjects:	Please specify NEXT PATIENT VISIT DATE (dd/mmm/yyyy):
☐ Yes ☐ No	

Site representative Name/Role: *(BLOCK LETTERS)*	**Signature**	**Date** *(DD-MMM-YYYY)*

2. To be reviewed by **Incyte Corporation Qualified staff:**

Based on the information provided please evaluate the temperature excursion data provided and confirm whether the affected product can be used / must be discarded.

Incyte Representative Name/Role: *(BLOCK LETTERS)*	**Signature**	**Date** *(DD-MMM-YYYY)*

IMPORTANT PXL CRA: Please ensure that response from sponsor is filed along with this Form in Investigator Site File and in PMED

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14.8. **APPENDIX H:** DEFINITION OF irRC

14.8.1. **Definition of Tumor Response Using irRC**

The sum of the products of diameters at tumor assessment using the irRC for progressive disease incorporates the contribution of new measurable lesions. Each net percentage change in tumor burden per assessment using irRC criteria accounts for the size and growth kinetics of both old and new lesions as they appear.

14.8.2. **Definition of Index Lesions Response Using irRC**

- **irComplete Response (irCR):** Complete disappearance of all index lesions. This category encompasses exactly the same subjects as "CR" by the mWHO criteria.
- **irPartial Response (irPR):** Decrease, relative to baseline, of 50% or greater in the sum of the products of the two largest perpendicular diameters of all index and all new measurable lesions (i.e., percentage change in tumor burden). Note: the appearance of new measurable lesions is factored into the overall tumor burden, but does not automatically qualify as progressive disease until the SPD increases by ≥ 25% when compared to SPD at nadir.
- **irStable Disease (irSD):** Does not meet criteria for irCR or irPR, in the absence of progressive disease.
- **irProgressive Disease (irPD):** At least 25% increase percentage change in tumor burden (i.e., taking sum of the products of all index lesions and any new lesions) when compared to SPD at nadir.

14.8.3. **Definition of Non-Index Lesions Response Using irRC**

- **irComplete Response (irCR):** Complete disappearance of all non-index lesions. This category encompasses exactly the same subjects as "CR" by the mWHO criteria.
- **irPartial Response (irPR) or irStable Disease (irSD):** non-index lesion(s) are not considered in the definition of PR, these terms do not apply.
- **irProgressive Disease (irPD):** Increases in number or size of non-index lesion(s) does not constitute progressive disease unless/until the percentage change in tumor burden increases by 25% (i.e., the SPD at nadir of the index lesions increases by the required amount).

14.8.4. **Impact of New Lesions on irRC**

New lesions in and by themselves do not qualify as progressive disease. However their contribution to total tumor burden is included in the SPD which in turn feeds into the irRC

criteria for tumor response. Therefore, new non-measurable lesions will not discontinue any subject from the study.

14.8.5. Definition of Overall Response Using irRC

Overall response using irRC will be based on these criteria:

- **Immune-Related Complete Response (irCR):** Complete disappearance of *all* tumor lesions (index and nonindex together with no new measurable/unmeasurable lesions) for at least 6 weeks from the date of documentation of complete response.
- **Immune-Related Partial Response (irPR):** The sum of the products of the two largest perpendicular diameters of all index lesions is measured and captured as the SPD baseline. At each subsequent tumor assessment, the sum of the products of the two largest perpendicular diameters of all index lesions and of new measurable lesions are added together to provide the Immune Response Sum of Product Diameters (irSPD). A decrease, relative to baseline of the irSPD compared to the previous SPD baseline, of 50% or greater is considered an irPR.
- **Immune-Related Stable Disease (irSD):** irSD is defined as the failure to meet criteria for immune complete response or immune partial response, in the absence of progressive disease.
- **Immune-Related Progressive Disease (irPD):** It is recommended in difficult cases to confirm PD by serial imaging. Any of the following will constitute progressive disease:
  - At least 25% increase in the sum of the products of all index lesions over baseline SPD calculated for the index lesions.
  - At least a 25% increase in the sum of the products of all index lesions and new measurable lesions (irSPD) over the baseline SPD calculated for the index lesions.

14.8.6. Immune-Related Response Criteria Definitions

Index Lesion Definition	Non-Index Lesion Definition	New Measurable Lesions	New Unmeasurable Lesions	Percent change in tumor burden (including measurable new lesions when present)	Overall irRC Response
Complete Response	Complete Response	No	No	-100%	irCR
Partial Response	Any	Any	Any	≥ -50%	irPR
				<-50% to <+25%	irSD
				>+25%	irPD
Stable Disease	Any	Any	Any	<-50% to <+25%	irSD
				>+25%	irPD
Progressive Disease	Any	Any	Any	≥+25%	irPD

14.8.7. Immune-Related Best Overall Response Using irRC (irBOR)

irBOR is the best confirmed irRC overall response over the study as a whole, recorded between the date of first dose until the last tumor assessment before subsequent therapy (except for local palliative radiotherapy for painful bone lesions) for the individual subject in the study. For the assessment of irBOR, all available assessments per subject are considered.

irCR or irPR determinations included in the irBOR assessment must be confirmed by a second (confirmatory) evaluation meeting the criteria for response and performed no less than 6 weeks after the criteria for response are first met.