Confidential

Protocol #: UC IRB17-1539
Version Date: 04/24/2019

SPONSOR: The University of Chicago

TITLE: A Phase II study of Epacadostat + Pembrolizumab in Head and Neck Cancer patients, who failed prior PD-1/PD-L1 therapy.

IND NUMBER: 133050

University of Chicago IRB#: IRB17-1539

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Version Date: PI-Ship change dated:04/24/2019

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1.0 TRIAL SUMMARY

Abbreviated Title	Pembrolizumab and Epacadostat in HNC
Trial Phase	*II*
Clinical Indication	Head and Neck Cancer (HNC)
Trial Type	Parallel single arm
Route of administration	Intravenously and oral
Trial Blinding	None, open label
Treatment Groups	Acquired Resistance Cohort / Suboptimal Benefit
Number of trial subjects	30
Estimated enrollment period	*18 months*
Estimated duration of trial	*24 months*

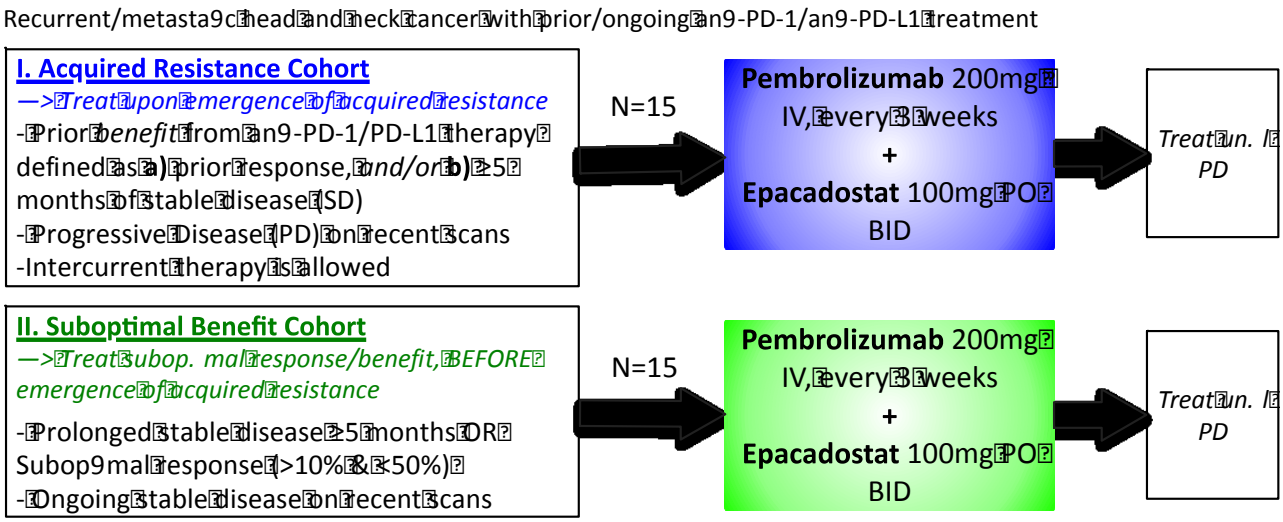
2.0 TRIAL DESIGN

2.1 Trial Design

Phase II, 2-cohort, single arm trial treated with the combination of the following two agents:

1. Pembrolizumab (MK3475) 200mg, every three weeks, iv
2. Epacadostat (INCB24360) 100mg, po BID

2.2 Trial Diagram



3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis

(1) **Objective:** Response Rate

Hypotheses:

Cohort 1: In patient with prior response to anti-PD-1/PD-L1+ therapy and subsequent (acquired) resistance combined IDO1 and PD-1 inhibition will re-induce responses.

Cohort 2: In patients with suboptimal benefit from prior anti-PD-1/PD-L1 therapy combined IDO1 and PD-1 inhibition will induce clinically meaningful responses.

3.2 Secondary Objective(s) & Hypothesis

(1) **Objective**: 1-year Progression-free (PFS) and Overall (OS) survival

Hypothesis: Combined PD-1 blockade with pembrolizumab + epacadostat in HNSCC patients will lead to improved 1-year survival in patients who a) progress on prior anti-PD-1/PD/L1 therapy on, and/or b) compared to patients who progress on 2nd line chemotherapy.

(2) **Safety**

Hypothesis: Combined treatment with pembrolizumab and epacadostat will be safe and tolerable in HNSCC patients.

3.3 Exploratory/Translational Objectives

(1) Interferon-gamma Gene Expression Profile (GEP) (*Seiwert ASCO 2015, Ribas ASCO 2015*) and evaluation of RR, PFS, and OS in GEP positive and GEP negative patients.

(2) Determine the micro-environment that underlies resistance/suboptimal treatment
a) underlying degree of tumor inflammation

b) Baseline PD-L1 expression

d) Determine underlying Interferon Gamma signature

(3) Assess underlying mutational burden (*Snyder 2014*))

Preclinical hypothesis: IDO1 inhibition will alter the micro-environment to a be "more T-cell inflamed" and make tumors amenable to benefit from anti-PD-1 treatment (when given concurrently with IDO1 inhibition). Hence we will evaluate tumors, with prior response exhibiting acquired resistance as well as tumors with minor/suboptimal benefit from prior PD-1/PD-L1 therapy for evidence (at baseline) of suboptimal immune microenvironmental conditions.

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the respective Investigator's Brochure (IB) for detailed background information on pembrolizumab and epacadostat.

4.1.1 Squamous Cell Carcinoma of the Head and Neck (HNSCC)

Squamous cell carcinoma of the head and neck (HNSCC) is the fifth most common malignancy worldwide and is comprised of *1) HPV-negative HNSCC (genetically closely resembling Lung SCC, triple negative breast cancer, bladder cancer),* and *2) HPV-positive HNSCC (resembling other virus associated tumors, e.g. cervical cancer, anal cancer, but also EBV-associated NPC, Merkel cell etc.)*(*HNC-TCGA, Nature 2015; Seiwert 2015*).

While HPV-positive tumors have a favorable outcome in the curative intent setting, once metastatic, prognosis remains poor. The incidence of HPV-positive HNSCC is increasing rapidly *(Chaturvedi 2011)*.

HNSCC shows some of the highest levels of a T-cell inflammation/tumor infiltrating lymphocytes. Based on TCGA data the top three tumor entities are melanoma, Head and Neck Cancer, and Lung Cancer (*HNC-TCGA 2015; Keck 2015).* Our group showed data defining this T-cell inflamed phenotype for HNSCC (*Saloura ASCO 2014*). Furthermore, there is widespread expression of multiple immune escape markers and PD-L1 expression is present in 70% of tumors (*Seiwert Lancet Oncology 2016; Saloura ASCO 2014*)

4.1.2 Immune Surveillance

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades (*Disis et al 2010*). 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.

The inability of the immune system to control tumor growth does not appear to result from an inability to recognize the tumor as foreign. Tumor cells have been shown to evade immune destruction despite displaying recognizable antigens on their surface and despite the presence of high-avidity T cells that are specific for these antigens (*Boon and van der Bruggen 1996, Ercolini et al 2005*). Histologic evaluation of many human cancers shows extensive infiltration by inflammatory and immune cells (*Galon et al 2006*), suggesting that the immune system responds to malignancy, albeit less effectively than needed to eradicate the tumors. These observations have led to the hypothesis that failure of the immune system to generate an effective response to malignancy

could be the result of inadequate stimulation or exaggerated negative regulation. A combination of immunotherapy agents that stimulate an immune response targeted to tumor cells combined with the relief of negative regulation should synergize in allowing the immune system to generate a response leading to enhanced tumor rejection.

4.1.3 Pharmaceutical and Therapeutic Background

Epacadostat (formerly INCB024360) represents a novel, potent, and selective inhibitor of the enzyme indoleamine 2,3 dioxygenase-1 (IDO1) in both human tumor cells and human dendritic cells (DCs). Pembrolizumab is a potent and highly selective humanized monoclonal antibody of the immunoglobulin (Ig)G4/kappa isotype directed against programmed death receptor 1 (PD-1). For a thorough discussion of the pharmacology of pembrolizumab and epacadostat, refer to the pembrolizumab Investigator's Brochure and the epacadostat Investigator's Brochure.

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

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

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on pembrolizumab.

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 Ig superfamily member related to CD28 and CTLA-4, which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). 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. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors. 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 non-hematopoietic 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. 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. 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 monoclonal antibody (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 States for the treatment of patients with platinum refractory head and neck squamous cell carcinoma on 8/5/2016) based on the Keynote 12 study data (*Seiwert et al 2016*)

4.1.4 Inhibition of PD-1 as a Target for Cancer

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

engagement of its ligands (PD-L1 and/or PD-L2) (*Talmadge et al 2007, Usubutun et al 1998*). The mechanism by which PD-1 down modulates T-cell responses is similar to but distinct from that of CTLA-4, as both molecules regulate an overlapping set of signaling proteins (*Hiraoka et al 2010, Nobili et al 2008*). PD-1 has been shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, Tregs, and natural killer cells (*Hodi et al 2010, Kloor et al 2009*). Expression has also been shown during thymic development on CD4-CD8- (double negative) T cells as well as subsets of macrophages and dendritic cells (*Hillen et al 2008*). The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including nonhematopoietic tissues as well as in various tumors (*Nobiliy et al 2008, Lee et al 2008 Leffers et al 2009, Nishimura et al 2000*). 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 (*Hodi et al 2010*). Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T- cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (*Liotta et al 2010*) and other cancers like head and neck cancer (*Seiwert et al 2016*). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

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

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

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

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

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

Within the context of cancer, there are several lines of evidence to suggest that IDO1 is a key regulator of the immunosuppressive mechanisms responsible for tumor escape from immune surveillance. Several groups have demonstrated that blockade of IDO1 activity can directly influence the ability of tumor-bearing animals to reject tumors (*Uyttenhove et al 2003, Muller et al 2005*). In addition, studies with 1-methyl-tryptophan, demonstrate that IDO1 inhibition dramatically increases the efficacy of various chemotherapeutic agents (e.g., platinum compounds, taxane derivatives, cyclophosphamide) without increased toxicity (*Muller et al 2005*). Although the specific mechanisms responsible for this potentiation remain to be fully elucidated, the effects were not observed in T- cell deficient animals, suggesting that the results may be the consequence of the disablement of immunosuppressive mechanisms that exist within the tumor microenvironment.

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

tolerance. Small molecule inhibitors of IDO1 may provide an innovative and tractable method to treat advanced malignancies either alone or in combination with chemotherapeutics and/or immunotherapy-based strategies.

4.1.6 Combined Immune Checkpoint Inhibition

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

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

On the basis of these observations, a Phase 3 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 objective response rate (ORR; according to modified World Health Organization criteria) for all patients in the concurrent-regimen group was 61% among subjects with BRAF wild-type tumors versus 11% in the ipilimumab alone group. Median duration of response had not been reached in either group. Median PFS had not been reached with the combination therapy and was 4.4 months for ipilimumab monotherapy. Grade 3 or 4 AEs occurred in 54% of subjects in the concurrent-regimen group and were 24% in the ipilimumab monotherapy group (*Postow et al 2015*). Common Grade 3 or 4 selected AEs that were related to the combination therapy included colitis (17%), diarrhea (11%), and an elevated alanine aminotransferase level (11%). Diarrhea (11%) was the most frequently reported Grade 3 or 4

AE associated with ipilimumab monotherapy, followed by colitis (7%). 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 (*Postow et al 2015*).

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

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

The IDO1 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 a study combining epacadostat and ipilimumab (INCB24360-201) subjects received ipilimumab (3 mg/kg IV every 3 weeks for 4 cycles) with epacadostat at doses of 25 mg BID, 50 mg BID continuous, 50 mg BID intermittent (2 wks on, 1 wk off), and 75 mg (50 mg q AM/25 mg q PM). 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, Grade 3 increased ALT/AST grade 3 colitis and grade 3 pneumonitis (n=1 each); 50 mg BID(intermittent), Grade 3 colitis (n=1); 75 mg, Grade 3 rash (n=1). The most common all Grade immune-related adverse events (irAEs) were rash (52%), pruritus (38%), diarrhea (33%), increased ALT (21%), increased AST (16%) hypothyroidism (12%) and colitis (10%). Grade ≥3 irAEs occurred in 23% of subjects. Grade ≥ 3 irAEs occurring in more than 1 subjects were increased AST and colitis (n=4 [9.5%] each). Among 32 immunotherapy-naïve subjects, ORR was 31% (10/32) per irRC and 28% (9/32) per RECIST and the CR rate per both criteria was 9.4%. At data cutoff, responses were ongoing in 6 subjects. The disease control rate (DCR; CR+PR+SD) was 62.5% per irRC and 53% per RECIST. Median PFS was 8.2 months by irRC and 5.3 months by RECIST. Among 10 subjects previously treated with immunotherapy, the DCR by both criteria was 30% (all SDs). In a study combining pembrolizumab and epacadostat (INCB 24360-202/ECHO-202) reported at ESMO 2016 (Ghangadhar et al), epacadostat combined with pembrolizumab showed a favorable objective response rate (58%), CR rate (26%), and disease control rate (74%), roughly on par with efficacy seen with nivolumab/ipilimumab in this early and small number dataset with a favorable side effect profile.

In summary, both IDO1 and PD-1 have been shown to suppress T-cell-mediated antitumor immunity, and IDO1 and the PD-1 ligand PD-L1 have been shown to be coexpressed in multiple cancer types and to correlate with poor prognosis. Combined inhibition of both pathways may therefore lead to greater suppression of antitumor immunity and to increased efficacy. Preclinical and early clinical data indicate that these pathways are important in melanoma as well as in other cancers, including NSCLC, HNSCC, and other tumor types.

4.1.7 PD-1 blockade in Head and Neck cancer (HNSCC)

PD-1 blockade was shown to be effective in HNSCC with a response rate of **16-18%** as reported recent in the Keynote 12 study *(Seiwert Lancet Oncology 2016, Chow et al JCO 2016*), with an estimated median overall survival of ~10-12months despite a heavily pretreated population (~60% of patients had 2 or more prior lines of therapy) compared to a

median overall survival of 10.1 months using the EXTREME regimen (platinum/5-FU/cetuximab) in first-line recurrent/metastatic HNSCC in a much more favorable first line population (*Vermorken NEJM 2008*).

Based on the Keynote 12 data Pembrolizumab received accelerated FDA approval as of August 5th 2016 by the FDA in the US.

Furthermore, evidence of long-term survival is seen in ~40% of patients (*Chow et al ESMO 2014*). However, a number of patients were also observed to eventually develop **acquired resistance** and some of those tumors with acquired resistance were biopsied and analysis is ongoing.

➔ ***Despite the prominent inflamed phenotype with widespread TIL infiltration and PD-L1 expression, HNSCC shows a lower rate of benefit from PD-1 blockade than melanoma, and acquired resistance/suboptimal benefit/treatment responses are prominent problems.***

Please refer to the Investigator's Brochure for additional Preclinical and Clinical data.

4.1.8 Preclinical and Clinical Study Data

Refer to the current Investigator's Brochures for additional details regarding pembrolizumab and epacadostat (iIB) for preclinical and clinical study data.

4.1.9 Ongoing Clinical Studies

Refer to the Investigator's Brochures (IBs) for pembrolizumab and epacadostat for preclinical and clinical study data.

4.2 Rationale

4.2.1 Rationale for combining PD-1 blockade with IDO inhibition in HNSCC.

IDO1 is a negative regulatory mechanism that contributes to tumor-derived immune suppression. In preclinical models, IDO1 inhibition has been shown to synergize with blockade of anti−PD-1/PD-L1 in delaying tumor growth and increasing OS (*Holmgaard 2013, Spranger 2013*). This effect was shown to be T-cell dependent, leading to enhanced T-cell proliferation and interleukin-2 production within the tumor and to a **marked increase in the effector-to-regulatory T cell ratios in the tumors**.

Epacadostat represents a novel, potent, and selective inhibitor of the enzyme indoleamine 2,3 dioxygenase 1 (IDO1) in both human tumor cells and human dendritic cells (DCs). For a thorough discussion of the pharmacology of epacadostat, refer to the epacadostat Investigator's Brochure (iIB).

While the majority of such patients with HNC can be treated with curative intent using multimodality approaches, a significant fraction of patients will fail therapy (typically within 12-18 months), especially those patients with high risk features such as advanced/bulky nodal stage, non-response to induction chemotherapy, residual disease on salvage surgery, and HPV-negative status.

HNSCC shows some of the highest levels of a CD3+/8+ lymphocyte infiltration (TILs), and T-cell inflammation, and multiple immune escape mechanisms are present (*Saloura/Seiwert, ASCO 2014, Lyford-Pike 2013*). PD-L1 expression is prominent in up to 70% of tumors, and similarly to other cancer type (*Powderly 2013*) correlates with response in the Keynote 12 study (*Seiwert, ASCO 2014/2015*) as well as a smaller cohort using the anti-PD-L1 antibody MEDI4636 (*Gibson ASCO 2015*).

Since pembrolizumab has shown significant single agent activity in HNC with a response rate of 16-18% (*Seiwert Lancer Oncology 2016; Chow JCO 2016*), excellent tolerability, and potentially affords long-term survival in a fraction of patients, further study of pembrolizumab, in particular combination aimed at overcoming acquired resistance or suboptimal benefit are indicated and clinically relevant.

4.2.2 Rationale for Dose Selection/Regimen/Modification

4.2.2.1 Justification of Treatment Regimen

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

study of pembrolizumab in combination with epacadostat. Reductions in tumor burden were seen in 15 of 19 evaluable subjects across doses of 25 mg BID to 100 mg BID in combination with pembrolizumab 2 mg/kg and 200 mg flat dosi ng. Objective responses were observed in all tumor types and all are ongoing and this combination has been well tolerated.

Based on a pharmacokinetic-pharmacodynamic model for epacadostat, nearly all patients' C_{avg} exceeded the IC_{50}, the range of active drug exposure seen in non-clinical models; further dose of 100 mg BID and above exceeded the IC50 at trough in nearly all patients [52].

The safety profile for the 300mg bid dose of epacadostat in combination with pembrolizumab in our 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 of 300mg epacadostat in combination with pembrolizumab is currently under study in all of Incyte's current protocols.

The dose combination of 100mg bid epacadostat plus pembrolizumab for our Phase III melanoma study (INCB24360-301) is based upon a benefit/risk assessment made specifically in melanoma in collaboration with Merck. In INCB24360-202, 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, Incyte believes that greater target coverage for inhibition of IDO1 may be necessary. Our 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. Incyte believes that greater target inhibition may be necessary in more resistant tumors, and potentially balances benefit/risk in favor of the higher epacadostat dose combination given that the dose does not exceed the MTD.

Based on observed systemic exposures and a pharmacokinetic-pharmacodynamic model for epacadostat, all patients who received 100 mg BID epacadostat in combination with pembrolizumab had time-averaged inhibition of IDO1 activity exceeding 50%, a level of PD activity associated with inhibition of tumor growth seen in non-clinical models. Dosing of 100 mg BID and above exceeded the IC50 at trough in nearly all patients [52]; further, the majority of patients had trough epacadostat exposures that were above the IC50 of IDO1 inhibition. Therefore, 100 mg BID was selected as the recommended Phase 2 dose for epacadostat in study INCB 24360-202 because this regimen had better tolerability as demonstrated by the Phase 1 safety data including fewer dose modifications (suspension and reductions) and resulted in consistent inhibition of IDO1. The overall experience of the epacadostat 1 00 mg BID dose in combination with pembrolizumab in study INCB 24360-202 supports this dose selected for the Phase 3 study INCB 24360-301.

4.2.2.2 Rationale for a fixed dose of Pembrolizumab

The dose of pembrolizumab planned to be studied in this study is 200 mg e very 3 weeks (Q3W). The dose recently approved in the United States for treatment of melanoma subjects is 2 mg/kg Q3W. Information on the rationale for selecting 200 mg Q3W is summarized below.

An open-label Phase I study (Keynote 001) is being conducted to evaluate the safety and clinical activity of single agent pembrolizumab. The dose escalation portion of this study evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) and dose expansion cohort evaluated 2 mg/kg Q3W and 10 mg/kg Q3W in subjects with advanced solid tumors. All dose levels were well tolerated and no 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. No MTD has been identified.

In Keynote 001, two randomized cohort evaluations (Cohorts B2 and D) of melanoma subjects receiving pembrolizumab at a dose of 2 mg/kg Q3W versus 10 mg/kg Q3W have been completed, and one randomized Cohort (Cohort B3) evaluating 10 mg/kg Q3W versus 10 mg/kg Q2W has also been completed. The clinical efficacy and safety data demonstrate a lack of clinically important differences in efficacy or safety profile at these doses. For example, in Cohort B2, advanced melanoma subjects who had received prior ipilimumab therapy were randomized to receive pembrolizumab at 2 mg/kg Q3W versus 10 mg/kg Q3W, and the objective response rate (ORR) was 28% (22/79) in the 2 mg/kg Q3W group and 28% (21/76) in the 10 mg/kg Q3W group (per RECIST 1.1 by independent central review). The proportion of subjects with drug-related adverse events (AEs), Grade 3-5 drug-related AEs, serious drug-related AEs, death or discontinuation due to an AE was comparable between groups. Cohort D which compared 2 mg/kg Q3W versus 10 mg/kg Q3W in advanced melanoma subjects naïve to ipilimumab also demonstrated overall similarity in efficacy and safety profile between two doses. In Cohort B3, advanced melanoma subjects (irrespective of prior ipilimumab therapy) were randomized to receive pembrolizumab at 10 mg/kg Q2W versus 10 mg/kg Q3W. The results demonstrate that the ORR was 35.0% (41/117) in the 10mg/kg Q2W group and 30.8% (33/107) in the 10 mg/kg Q3W group (per RECIST 1.1 by independent central review) (cut-off date of 18-April-2014). The proportion of subjects with drug-related AEs, Grade 3-5 drug- related AEs, serious drug related AEs, death or discontinuation due to an AE was comparable between groups.

An integrated body of evidence suggests that 200 mg every 3 weeks (Q3W) is expected to provide similar response to 2 mg/kg Q3W, 10 mg/kg Q3W and 10 mg/kg every 2 weeks (Q2W). Previously, a flat pembrolizumab exposure-response relationship for efficacy and safety has been found in subjects with melanoma in the range of doses between 2 mg/kg and 10 mg/kg. Exposures for 200 mg Q3W are expected to lie within this range and

will be close to those obtained with 2 mg/kg Q3W dose. 2 mg/kg Q3W is the approved dose for metastatic melanoma in the US.

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

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

4.2.3 Translational Rationale

The micro-environmental changes responsible for resistance to PD-1/PD-L1 blockade are incompletely understood. We will evaluate baseline tissue (archival or freshly obtained) for evidence of factors that may correlate with acquired resistance/suboptimal benefit as related to the immune microenvironment/tumor inflammation/IDO.

HNSCC is a disease with oftentimes biopsy accessible tumors, and baseline biopsies are optional (if archival tissue is available) or mandatory if no archival tissue is available.

Core biopsies (3-5 cores) will be obtained at baseline as indicated (see above/eligibility). An on treatment biopsy at 2-4 weeks on treatment will considered / is optional and dependent on ability to safely biopsy the tumor. Also in patients who have benefit and subsequently progress (acquired resistance) a biopsy may be considered.

4.2.4 Rationale for Endpoints

4.2.4.1 Efficacy Endpoints

Primary Endpoint: Response Rate is a widely used and accepted marker of activity, and especially in a setting of prior PD-1/PD-L1 treatment failure is expected to be a robust outcome measure. For immunotherapy agents generally speaking response rate may underestimate the benefit (namely survival) as many patients with stable disease still achieve improved or prolonged survival.

Secondary Endpoint: Overall Survival (e.g. 1-year overall survival is an acceptable early outcome measure to estimate survival in a poor prognosis patient population with an estimate median overall survival of ≤6 months and ~30% of patients alive at one year (*Stewart 2009*)).

4.2.4.2 Biomarker Research

In an effort to identify those patients who may be more likely to respond to pembrolizumab, baseline tumor samples will be evaluated for PD-L1 expression as well as other markers using an IHC or IF assay. This work will be done retrospectively.

Furthermore, patient samples will be analyzed retrospectively for GEP scoring using the Nanostring platform.

Based on data from hundreds of patients in numerous pembrolizumab studies in multiple cancer types, these biomarkers may potentially be predictive of patient benefiting from adjuvant pembrolizumab. The purpose of this trial is to assess whether potential benefit from adjuvant therapy is also related to PD-L1 and/or GEP biomarkers.

A key question of this study is whether IDO inhibition combined with PD-1 inhibition is more effective in PD-L1 expressing / GEP positive tumors or whether this combination is able to overcomes the less inflamed phenotype and lead to a response in PD-L1 negative/GEP low patients.

4.3 Benefit/Risk

4.3.1.1 Risk from Epacadostat

In 28-day toxicology studies, C_{max} values have exceeded the IC_{50} for the IDO1 enzyme in cells (7 nM) by up to 370-fold, and the IC_{50} for the vasopressin 1a receptor by up to 40 -fold (130-fold in single dose studies) in the absence of any toxicity, so the risk of unintended pharmacological activity is expected to be low. In the Phase 1 clinical study in subjects with refractory solid tumors (INCB 24360-101) doses up to 700 mg BID were given without an MTD determined. Epacadostat was well tolerated with a single SAE of exacerbated radiation pneumonitis in a subject with metastases treated at 300 mg BID, 1

report of asymptomatic and reversible hypopituitarism despite continued administration of epacadostat, and 1 event of Grade 3 fatigue determined by the investigator to be related to study drug and considered a DLT in the 400 mg BID dose group.

Theoretically, inhibition of IDO1 could cause an increase in serotonin levels that could precipitate a cluster of AEs termed serotonin syndrome (SS) when administered in combination with other serotonergic agents. This rare syndrome has been associated with some monoamine oxidase inhibitors (MAOIs) and combinations of serotonergic drugs [53]. The clinical manifestations of SS range from barely perceptible to lethal; onset is rapid (within 12 hours of drug(s) administration). Based on preliminary studies in the rat, concentrations of epacadostat in the cerebrospinal fluid were below the quantifiable limit of detection (2 nM) after IV dosing, and total brain homogenate concentrations were approximately 15% of corresponding plasma concentrations. Therefore, epacadostat exhibits apparent limited penetration across the blood- brain barrier and is likely not associated with significant effects on tryptophan metabolism in the brain that might impact brain serotonin levels. This represents a hypothetical risk only and has not been observed in any clinical studies of epacadostat with over 600 subjects treated to date. Twelve subjects in the INCB 24360-201 combination study with ipilimumab were receiving concomitant treatment with an SSRI without any consequences. Although the risk is theoretical, use of MAOIs will be prohibited during the study and all subjects will be provided with an informative subject leaflet describing the signs and symptoms of the syndrome along with instructions to seek immediate medical care if any of these signs or symptoms are observed.

4.3.1.2 Risk from Pembrolizumab

An open-label Phase I study (Protocol 001) is being conducted to evaluate the safety and clinical activity of single agent pembrolizumab. The dose-escalation portion of this study evaluated 3 dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks in subjects with advanced solid tumors. All 3 dose levels were well tolerated and no DLTs were observed. Based on pharmacokinetic (PK) data showing a half-life of 21 days, the Protocol was amended to include a dosing frequency of every 3 weeks in expansion cohorts. Of a total of 479 subjects, who have received pembrolizumab in Protocol 001, 466 (97.3%) experienced treatment-emergent AEs, of which 368 (76.8%) were considered drug-related. Serious AEs were reported in 30.1% of subjects, but SAEs that were attributed as potentially (possibly, probably, or definitely) drug-related by investigators were reported in 6.7% of subjects overall. Potential irAEs have been observed, including pneumonitis in both melanoma and NSCLC cohorts. The most commonly reported treatment-emergent AEs experienced have been fatigue, nausea, cough, pruritus, diarrhea, and rash. Most subjects continued treatment despite of AEs, and only 4.2% of subjects discontinued study treatment because of an AE that was considered related to study treatment by investigators. Thus, the overall AE summary suggests that pembrolizumab is generally tolerable, and AEs are generally manageable in subjects.

4.3.1.3 Risk from combined Pembrolizumab and Epacadostat

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

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

The most frequently reported (≥ 15%) adverse events (AEs) of any grade for the combined Phase 1 and Phase 2 treatment groups (n=117) treated with epacadostat 100 mg BID were fatigue (35.0%), constipation (24.8%), diarrhea (20.5%), nausea (20 .5%), vomiting (18.8%), pyrexia (16.2%) and dyspnea (15.4%). Fatigue (13.7%) and rash (11.1%) (including the preferred terms rash, rash maculopapular, rash generalized, and rash macular) were the only treatment-related AE reported in > 10% of subjects. Treatment-related AEs of rash were only reported in the Phase 2 group.

Any Grade 3/4 AEs occurring in more than 1 subjects in the combined Phase 1 and Phase 2 epacadostat 100 mg BID group include: rash (n=5, 4.3%), dehydration (n=4 3.4%), nausea, vomiting and AST increased, (n= 3 each, 2.6%), diarrhea, small intestine obstruction, fatigue, lipase increased, hypercalcemia, hyponatremia, tumour pain, and pneumonia aspiration (n=2 each, 1.7%). Treatment-related AEs ≥ Grade 3 occurring in more than one subject included rash (5 subjects, 4.3%) and dehydration, lipase increased, AST increased and nausea (2 subjects [1.7%] each).

In subjects receiving epacadostat 300 mg BID, there was an observable trend in increased adverse events of rash (total events as well as severity) and the number of required dose holds and dose reductions for epacadostat, compared to subjects receiving 100 mg BID.

Although the rashes observed at the 300 mg BID dose level were reversible with dose interruptions and medical treatment, total dose interruptions were higher in the 300 mg BID group with 5/19 interrupting epacadostat and 3 requiring dose reductions due to adverse events compared to 1 subject in 100 mg BID requiring a dose interruption, 2 subjects in 50 mg BID and 1 subject in 25 mg BID. Based on the risk for early progression during dose interruptions and dose reductions associated with epacadostat 300 mg BID in combination with pembrolizumab 200 mg IV Q3 weeks, 100 mg BID was selected as the dose for use in a proposed Phase 3 study.

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying pembrolizumab and epacadostat Investigators Brochures (IBs) and Informed Consent documents.

5.0 METHODOLOGY

5.1 Entry Criteria / Eligibility

5.1.1 Diagnosis/Condition for Entry into the Trial

5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must fulfill the following entry criteria:

1. Patients must have histologically confirmed squamous cell carcinoma of the head and neck (unresectable and not amenable to curative intent therapy)
2. Meet criteria for either the Acquired Resistance OR the Suboptimal Benefit Cohort
    a. **Acquired Resistance is defined as (i and ii must both be met):**
        i. **Prior *benefit* from anti-PD-1/PD-L1 therapy defined as a) prior response, *and/or* b) ≥5 months of stable disease (SD). Intervening therapies are allowed.**
        ii. **Progressive Disease (PD) on recent scans**
    b. **Suboptimal Benefit is defined as (i and ii must both be met):**
        i. **Prolonged stable disease ≥5 months OR Suboptimal response (>10% & <50% shrinkage per RECIST at any evaluation timepoint)**
        ii. **Ongoing stable disease on recent scans**
        iii. **Last treatment with an anti-PD-1/PD-L1 agent within 6 weeks prior to starting protocol treatment**
3. Archival tissue for PD-L1 staining (alternatively a new biopsy (core) at baseline can be used). A minimum of 10 slides is required (unless approval from the PI is obtained)
4. Measurable disease per RECIST 1.1.
5. Known HPV status
6. ECOG performance status 0 or 1
7. Be willing and able to provide written informed consent/assent for the trial.
8. Be ≥ 18 years of age on day of signing informed consent.
9. Demonstrate reasonable organ function as defined in
10. Table **1**, all screening labs should be performed within 10 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 clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥40 mL/min for subject with creatinine levels > 2.0 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.2 X ULN **OR** in case of Gilbert's disease an elevated total Bilirubin is allowed if direct Bilirubin is ≤40% of total
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN
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.	

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

12. Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 5.7.2). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

13. Male subjects 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.

5.1.3 Subject Exclusion Criteria

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

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 2 weeks of the first dose of treatment.

2. 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 trial treatment.

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

4. Has hypersensitivity to pembrolizumab, epacadostat or any of its excipients.

5. Has had a prior anti-cancer monoclonal antibody (mAb) within 3 weeks prior to study Day 1, or targeted small molecule therapy within 2 weeks prior to study Day 1, or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.

6. Has not recovered from prior surgery, chemotherapy or radiation therapy from adverse events due to a previous treatment/ administered agent (i.e., ≤ Grade 1 or return to baseline prior to treatment).

    - Note: Subjects with ≤ Grade 2 neuropathy, any grade hearing loss or tinnitus, or typical side effects from radiotherapy are an exception to this criterion and may qualify for the study.

    - Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

7. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer or any tumors that are not likely to influence live expectancy in the subsequent 3 years without active treatment (e.g. low grade prostate cancer in absence of therapy).

8. Has known active (=growing) central nervous system (CNS) metastases and/or carcinomatous meningitis. Radiation or resected brain metastasis are acceptable if clinically stable.

9. 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 (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

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

11. Warfarin use, even if low dose warfarin is <u>not</u> acceptable. However, other anti-coargulants (e.g. aspirin, enoxaparin and heparin derivatives, thrombin inhibitors, etc) are acceptable.

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

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

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

15. Has received prior therapy with an IDO inhibiting agent.

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

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

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

19. Subjects receiving MAO-inhibitors (MAOI) or drug which has significant MAOI activity (meperidine, linezolid, methylene blue) within the 21 days before screening.

20. Any history of Serotonin Syndrome after receiving serotonergic drugs.

21. History or presence of an abnormal electrocardiogram (ECG) that, in the investigator's opinion, is clinically meaningful. Screening QTc interval > 470 milliseconds is excluded. In the event that a single QTc is > 470 milliseconds, the subject may enroll if the average QTc for the 3 ECGs is < 470 milliseconds. For subjects with an intraventricular conduction delay (QRS interval > 120 milliseconds), the JTc interval may be used in place of the QTc with sponsor approval. The JTc must be < 340 milliseconds if JTc is used in place of the QTc. Subjects with left bundle branch block are excluded.

    Note: QTc prolongation due to pacemaker may enroll if the JTc is normal.

22. Use of any UGT1A9 inhibitor from screening through follow-up period, including the following: diclofenac, imipramine, ketoconazole, mefenamic acid, and probenecid. See Section 5.11 for more details.

23. History of organ transplant that requires use of immunosuppressives.

24. Any condition that would jeopardize the safety of the subject or compliance with the Protocol.

25. Clinically significant cardiac disease, including unstable angina, acute myocardial infarction within 6 months from Day 1 of study drug administration, New York Heart Association Class III or IV congestive heart failure, and arrhythmia requiring 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 within 30 days prior to initiation of treatment.

5.2 Trial Treatments

The treatment to be used in this trial is outlined below in Table 2

Table 2 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	**200 mg mg/kg**	**Q3W**	**IV infusion**	**Day 1 of each 3 week cycle**	**Experimental**
Epacadostat	**100mg**	**Daily, BID**	**PO**	**continuous**	**Experimental**

Treatment Period: Both Epacadostat and Pembrolizumab are given concurrently.

Trial treatment should initiate as soon as PD-L1 status and cohort allocation are known

5.2.1 Dose Selection

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background and Rationale.

Details on preparation and administration of pembrolizumab (MK-3475) and Epacadostat are provided in the respective Pharmacy Manuals.

5.3 Dose Modifications

Adverse events (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. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 3 below. See below for supportive care guidelines, including use of corticosteroids.

Table 3: Dose Modification Guidelines for Drug-Related Adverse Events for Pembrolizumab and Epacadostat

Toxicity	Hold Treatment For Grade	Agent	Timing for Restarting Treatment	Dose Level for	Treatment Discontinuation
Diarrhea/Colitis	2-3	Pembrolizumab	Toxicity resolves to Grade 0-1	n/a	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

		Epacadostat	Toxicity resolves to Grade 0-1	Related: Reduce by 1 dose level Not Related: Same dose level	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
	4	Pembrolizumab	Permanently discontinue	n/a	Permanently discontinue
		Epacadostat	Permanently discontinue	n/a	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Pembrolizumab	Toxicity resolves to Grade 0-1	n/a	Toxicity does not resolve within 12 weeks of
		Epacadostat	Toxicity resolves to Grade 0-1	Related: Reduce by 1 dose level Not Related: Same dose level	Toxicity does not resolve within 12 weeks of last dose
	3-4	Pembrolizumab	Permanently discontinue	n/a	Permanently discontinue
		Epacadostat	Permanently discontinue	n/a	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyper-glycemia	T1DM or 3-4	Pembrolizumab	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure	n/a	Resume pembrolizumab when subjects are clinically and metabolically stable
		Epacadostat	Toxicity resolves to Grade 0-1	Related: Reduce by 1 dose level Not Related: Same dose level	Resume epacadostat when subjects are clinically and metabolically stable

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 of the scheduled interruption, unless otherwise discussed with the PI. The reason for interruption should be documented in the patient's study record.

5.3.1 Criteria and Procedures for Treatment Interruption

In some circumstances, it may be necessary to temporarily interrupt both study treatments as a result of AEs that may have an unclear relationship to study drug. Any interruptions of > 2 weeks or for LFT abnormalities must be discussed with the medical monitor before resuming

treatment. Treatment with both study drugs should be withheld for drug-related Grade 4 hematologic toxicities, nonhematological toxicity ≥ Grade 3 (including laboratory abnormalities), and severe or life-threatening AEs (see Table 3). Table 3 summarizes the dosing actions for MK-3475 and INCB024360 that must be implemented with the indicated related AEs. Additional information related to dose changes for INCB024360 and MK-3475 can be found in subsequent Sections.

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

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

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

5.3.2 Procedures for Subjects Exhibiting Immune-Related Adverse Events

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

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

If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes before labeling an AE as an irAE. Information on how to identify and evaluate irAEs has been developed and is included in the Event of Clinical Interest and Immune-Related Adverse Event Guidance Document. Subjects who develop a ≥ Grade 2 irAE should be discussed immediately with the PI.

Recommendations for management of specific immune-mediated AEs such as pneumonitis enterocolitis, and hepatitis are detailed in the sections below.

Table 4: General Approach to Handling Immune-Related Adverse Events

irAE	Withhold/Discontinue Pembrolizumab (MK-3475) and Epacadostat	Supportive Care
Grade 1	No action.	Provide symptomatic treatment.
Grade 2	May withhold MK-3475 and INCB024360. Subjects with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician's 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 to 1 within 12 weeks of the last dose.	Consider systemic corticosteroids in addition to appropriate symptomatic treatment.
Grade 3 or severe	Withhold MK-3475 and INCB024360. Discontinue if unable to reduce corticosteroid dose to < 10 mg/day prednisone equivalent within 12 weeks of toxicity or permanently discontinue for any severe or ≥ Grade 3 drug-related AE that recurs or any life-threatening event. For grade 3 rash, dose interruption and topical treatment (see next column) until resolution are recommended Resume at same dose although dose reduction in cases of persistent rash can be considered	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. Topical steroids per physician choice (e.g. hydrocortisone, or stronger). Typically oral steroids are not required.
Grade 4	Permanently discontinue	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment.

5.3.3 Timing of Dose Administration of Epacadostat.

Epacadostat will be administered orally BID every 12 hours without regard to food at the dose identified in this study. If a dose is missed by more than 4 hours, that dose should be skipped and the next dose should be taken at the next scheduled timepoint. All BID doses will be taken in the morning and evening, approximately 12 hours apart.

Subjects will begin treatment with epacadostat on Day 1 of the study and will continue administration through the evening prior to the scheduled date of the subject's post-treatment visit. Subjects should plan to take the AM dose of epacadostat on clinic days also at the same time. There is no priority to the order of administration of epacadostat and pembrolizumab when administered in combination; however, the dose of epacadostat should be taken as close to the regularly scheduled 12-hour dosing interval as possible.

5.3.4 Supply, Packaging, and Labeling of Epacadostat

Epacadostat will be available as 25, or 100 mg tablets packaged in high-density polyethylene bottles. All tablet excipients comply with the requirements of the applicable compendial monographs (Ph. Eur., USP/NF) (refer to the iIB). All Incyte investigational

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

5.3.5 Storage and Dispensing of Epacadostat

Clinical supplies must be stored as described in the iIB.

An initial bulk supply of epacadostat will be provided to investigative sites prior to enrollment of the first subject. When dispensing to subjects, the investigator or designee will remove the appropriate quantity of epacadostat from their stock, dispense the medication, and enter the amount dispensed into the CRF and drug accountability log.

5.3.6 Timing of Dose Administration of Pembrolizumab.

Combination treatment (during treatment period) should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

→ All trial treatments will be administered on an outpatient basis.

Pembrolizumab 200 mg will be administered as a 30-minute IV infusion every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. . Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

5.3.7 Trial Blinding/Masking

This is an open label trial without randomization.

5.4 Treatment Allocation

Please see eligibility / Inclusion criteria for allocation to one of the two cohorts.

5.5 Stratification

There will be no stratification

5.6 Concomitant Medications/Vaccinations (allowed & prohibited)

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

5.6.1 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.

5.6.2 Restricted Medications and Measures

None, see 5.6.3 prohibited concomitant medications

5.6.3 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Use of coumarin-based anticoagulants (eg, Coumadin®) is not allowed. Alternatives to coumarin-based anticoagulants should be considered and are acceptable.
- Radiation therapy
    - Note: 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 trial treatment and while participating in the trial. 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. The use of physiologic doses of corticosteroids may be approved after consultation with the PI (typically ≤10mg of Prednisone or equivalent).

- 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 epacadostat has been taken (see Appendix C).

- Any UGT1A9 inhibitor, including acitretin, amitriptyline, androsterone, cyclosporine, dasatinib, diclofenac, diflunisal, efavirenz, erlotinib, estradiol (17-beta), flutamide, gefitinib, gemfibrozil, glycyrrhetinic acid glycyrrhizin, imatinib, imipramine, ketoconazole, linoleic acid, mefenamic acid, mycophenolic acid, niflumic acid, nilotinib, phenobarbital, phenylbutazone, phenytoin, probenecid, propofol, quinidine, ritonavir, Sorafenib, sulfinpyrazone, valproic acid, and verapamil.

- NOTE: Propofol, when used for short-term sedation during surgical/biopsy procedures, is allowed after consultation with the medical monitor. The epacadostat dose may be taken on the morning of the procedure, and the evening dose held following the procedure. Epacadostat may be resumed the next day.

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

The Exclusion Criteria may describe other medications, which are prohibited in this trial.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.7 Rescue Medications & Supportive Care

5.7.1 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below and in greater detail in the ECI guidance document. 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.

Note: if after the evaluation the event is determined not to be related, the investigator is instructed to follow the ECI reporting guidance but does not need to follow the treatment

guidance (as outlined in the ECI guidance document). Refer to Section 5.2.1 for dose modification.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event. Suggested conditional procedures, as appropriate, can be found in the ECI guidance document.

- **Pneumonitis**:
    - For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
    - For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
    - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

- **Diarrhea/Colitis**:
  Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

    - All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
    - For **Grade 2 diarrhea/colitis** that persists greater than 3 days, administer oral corticosteroids.
    - For **Grade 3 or 4 diarrhea/colitis** that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.
    - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**

    - For **T1DM** or **Grade 3-4** Hyperglycemia
        - 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.

- **Hypophysitis**:
    - For **Grade 2** events, treat with 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.
    - For **Grade 3-4** events, treat with an initial dose of IV corticosteroids 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.

- **Hyperthyroidism or Hypothyroidism**:
  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.
    - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
        - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
        - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
    - **Grade 3-4** hyperthyroidism
        - 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.

- **Hepatic**:
    - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
        - Treat with IV or oral corticosteroids
    - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
    - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

- **Renal Failure or Nephritis**:
    - For **Grade 2** events, treat with corticosteroids.
    - For **Grade 3-4** events, treat with systemic corticosteroids.
    - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Management of Infusion Reactions**: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Table 5 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 5 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

5.7.2 Procedures for Subjects Exhibiting Serotonin Syndrome

As noted in the background, there is a theoretical chance that Epacadostat/INCB024360 could cause an increase in serotonin levels in the brain that might trigger SS (*Boyer and Shannon 2005*) 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 described, including tremor; hyperreflexia; spontaneous, ocular, or inducible clonus; together with agitation, fever, diaphoresis, or muscle rigidity:

- Immediately interrupt Epacadostat/INCB024360 administration. Administration of Pembrolizumab/MK-3475 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 INCB024360 after the SSRI or SNRI has been discontinued, no sooner than 5 half-lives have elapsed for the specific SSRI or SNRI in question, and after resolution of signs/symptoms of SS.
The SSRI or SNRI dosing MAY NOT be
restarted.
- If subject chooses to withdraw from the study, or must restart treatment with SSRI or SNRI, the subject should be scheduled for a follow-up visit. Treatment with SSRI or SNRI may be initiated 2 weeks after resolution of signs and symptoms of SS.

5.7.3 Treatment After Initial Evidence of Radiologic Evidence of Disease Progression

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

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

When feasible, subjects should not be discontinued until progression is confirmed; however, the decision to continue study treatment after the first evidence of disease progression is at the investigator's discretion based on the clinical status of the subject as described in Table 6.

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

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

Table 6: Imaging and Treatment After First Radiologic Evidence of Progressive Disease

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

5.8 Diet/Activity/Other Considerations

5.8.1 Diet

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

5.8.2 Contraception

Pembrolizumab and epacadostat 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. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

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 they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.8.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, 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 the Sponsor and to Merck/Incyte without delay and within 24 hours to the Sponsor and within 2 working days to Merck/Incyte, as described in section 10.7, if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and to Merck/Incyte and followed as described above and in Section 7.2.2.

5.8.4 Use in Nursing Women

It is unknown whether pembrolizumab 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.

5.9 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 7.1.4 – Other Procedures.

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

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed radiographic disease progression (=2nd scan within 4-8 weeks)

  Note: For unconfirmed radiographic disease progression, please see Section 5.7.3

  Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved, please see Section 5.7.3
- Unacceptable adverse experiences as described in Section 5.2.1.2
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 12 months of uninterrupted treatment with pembrolizumab or 18 administrations of study medication, whichever is later.

- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 6 (Protocol Flow Chart) and Section 7.1.5 (Visit Requirements). After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 7.2.3.1). 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, the end of the study, or 2 years beyond the last administration of study drug, whichever occurs first.

5.9.1 Discontinuation of Study Therapy after CR

For subjects who have **overt disease** at any point during study treatment, discontinuation of treatment may be considered if they attain a **confirmed** CR AND have been treated for at least 24 weeks with pembrolizumab 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 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/Exclusion criteria, and the trial is open. Subjects will resume therapy at the same dose and schedule at the time of initial discontinuation. Additional details are provided in Section 7.1.5.5.

5.10 Subject Replacement Strategy

Patients who receive 0, or only 1 dose only will be replaced due to inadequate treatment exposure. An intention to treat analysis will be performed as a secondary analysis, but for the primary analysis only patients with adequate treatment exposure to 2 or more doses of pembrolizumab will be included.

5.11 Clinical Criteria for Early Trial Termination

Early trial termination at a participating site will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete

2. Poor adherence to protocol and regulatory requirements

3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects

4. Plans to modify or discontinue the development of the study drug

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

6.0 TRIAL FLOW CHART

6.1 Study Flow Chart

Trial Period:	**Screening Phase**			**Treatment Cycles***								**End of Treat-ment**	**Post-Treatment**		
Treatment Cycle/Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2)		1	2	3	4	To be repeated beyond 8 cycles **				Discontinuation (D/C)	Safety Follow-up	Follow Up Visits	Survival Follow-Up
								5	6	7	8				
Scheduling Window (Days):		-28 to -1			± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of D/C	30 days post D/C	Every 8 weeks post D/C	Every 12 weeks
Administrative Procedures															
Informed Consent	X														
Inclusion/Exclusion Criteria	X	X													
Demographics and Medical History	X	X													
Prior and Concomitant Medication Review	X	X		X	X	X	X	X	X	X	X	X			
Trial Treatment Administration				X	X	X	X	X	X	X	X				
Post-study anticancer therapy status												X			
Survival Status												X	X	X	X
Clinical Procedures/Assessments															
Epacadostat administration (daily po)				*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*				
Pembrolizumab administration (iv q3 weeks)				*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*				
Review Adverse Events				X	X	X	X	X	X**	X	X**	X			
Full Physical Examination		X		X		X		X	X**		X**	X	X	X	
Vital Signs and Weight		X		X	X	X	X	X	X	X	X	X	X	X	
ECOG Performance Status		X		X	X	X	X	X	X**	X	X**	X	X	X	

Trial Period:	**Screening Phase**			**Treatment Cycles***								**End of Treat-ment**	**Post-Treatment**		
Treatment Cycle/Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2)		1	2	3	4	To be repeated beyond 8 cycles **				Discontinuation (D/C)	Safety Follow-up	Follow Up Visits	Survival Follow-Up
								5	6	7	8				
Scheduling Window (Days):		-28 to -1			± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of D/C	30 days post D/C	Every 8 weeks post D/C	Every 12 weeks
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory															
For Women of childbearing potential - Pregnancy Test – (continued) Urine or Serum β-HCG (also see Table 9, page 37)		X													
PT/INR and aPTT		X													
CBC with Differential		X		X	X	X	X	X	X	X	X	X	X	X	
Comprehensive Serum Chemistry Panel		X		X	X	X	X	X	X	X	X	X	X	X	
Urinalysis		X													
T3, FT4 and TSH		X						X				X			
Efficacy Measurements															
Tumor Imaging (every 8 weeks)		X		Every 8 weeks										X	
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood															
Archival (or Newly Obtained) Tissue Collection (typically FFPE, ≥10 tumor containing 5-micron slides to be collected) If NOT available will require a new biopsy (not FNA) unless biopsy is not safe/technically	X														

Trial Period:	**Screening Phase**			**Treatment Cycles***								**End of Treat-ment**	**Post-Treatment**		
Treatment Cycle/Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2)		1	2	3	4	To be repeated beyond 8 cycles **				Discontinuation (D/C)	Safety Follow-up	Follow Up Visits	Survival Follow-Up
								5	6	7	8				
Scheduling Window (Days):		-28 to -1			± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of D/C	30 days post D/C	Every 8 weeks post D/C	Every 12 weeks
feasible															
Correlative Studies Blood Collection including a) germline DNA collection and b) PAXgene tube for RNA		X[2,3]			X[3]										

1. The fresh biopsy/FNA requirement can be waived under extenuating circumstances after approval by the PI (Dr. Pearson) e.g such a procedure is not safe or technically feasible.

If clinically indicated tissue from a biopsy will also be banked using the UCCCC# 8980 banking protocol.

2. -- 2 Purple top tubes, blood volume, processing etc will follow HTRC SOPs

3. – PAXgene tube, blood volume, processing etc will follow HTRC SOPs

** Treatment cycle length = 21 days*

*** After cycle 8, as clinically appropriate ECOG performance status, physical exam, and adverse event recording interval may be increased to every other cycle (=every 6 weeks).*

End of Treatment = end of 2 years of treatment OR progressive disease as outlined in prior section.

Survival follow-up can be done via phone if patient is not coming in for additional care

Laboratory tests for screening or potentially a Second Treatment Course should be performed within 14 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor and/or Merck/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.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The Investigator must obtain documented consent from each potential subject prior to participating in a clinical trial.

7.1.1.1.1 General Informed Consent

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

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

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

The informed consent will adhere to IRB requirements and applicable laws and regulations.

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

7.1.1.4 Prior and Concomitant Medications Review

7.1.1.4.1 Prior Medications

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

7.1.1.4.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

7.1.1.5 Disease Details and Treatments

7.1.1.5.1 Disease Details

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

7.1.1.5.2 Prior Treatment Details

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

7.1.1.5.3 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial 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.

7.1.1.6 Assignment of Randomization Number

Not applicable, this is an open label, non-randomized trial

7.1.1.7 Trial Compliance (Medication/Diet/Activity/Other)

Patients are expected to follow the outlined treatment schedule, and violation of trial procedures may lead to trial discontinuation (see Section 5.8) if compliance is felt to impact treatment in a meaningful way or interpretability of data (consultation with the PI recommended).

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

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

Please refer to section 7.2 for detailed information regarding the assessment and recording of AEs.

Safety assessments will consist of monitoring and recording all adverse events and serious adverse events, the regular monitoring of hematology, blood chemistry and urine values, regular measurement of vital signs and the performance of physical examinations.

These assessments should be performed within ±7 days of the scheduled day of assessment except for adverse events that will be evaluated continuously through the study. Safety and tolerability will be assessed according to the NIH/NCI CTC http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or abnormal laboratory value suspected to be related to treatment must be followed at least weekly until the adverse event or abnormal laboratory resolves or returns to grade 1. If a patient requires a dose delay of >16 weeks from the intended day of the next scheduled dose, then the patient must be discontinued from the study.

7.1.2.2 Full Physical Exam

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,

7.1.2.3 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 6.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

7.1.2.4 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 11.1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

7.1.2.5 Tumor Imaging and Assessment of Disease

Tumor imaging will be performed as outline in the flowchart under Section 6, typically every 8-16 weeks or as clinically indicated.

Radiologic recurrence/progression of disease should be confirmed 4-8 weeks after the initial scan and patients can continued treatment until confirmation if clinically stable and no other immediate reason for discontinuation is present.

Whenever possible clinical progression should be confirmed radiologically.

7.1.2.6 Tumor Tissue Collection and Correlative Studies Blood Sampling

A minimum of 10 slides (from the original tumor prior to initiation of curative intent therapy) will be collected.

Blood will be obtained at baseline and at the time of the second treatment. Please see tissue/blood collection SOP provided separately.

7.2 Research Tests

Tissue obtained (PRIOR to curative intent therapy) from the diagnostic biopsy/panendoscopy and/or during surgical resection, and whole blood samples (in PAXGene tubes).

The correlative work will be performed/coordinated at the University of Chicago, and may be done with collaborators e.g. at Incyte or Merck.

7.2.1 Sample Shipping

All the tissue, whole blood and serum samples will be collected in the HTRC and additional details will be provided in a brief Tissue/Blood SOP that will be continually updated.

7.2.2 IHC staining

→ Multicolor immunohistochemistry will be performed and results will be descriptive and presented in tabular with a focus on highlighting changes from pre- treatment samples.

Markers will include PD-L1 (research), and CD8.

Initial PD-L1 for allocation to a sample group will be done using the DAKO 22C3 CLIA assay for PD-L1 staining.

Additional staining for FOXP3, CD163, IDO, CD206, CD11a, CD163, and related markers if appropriate based on assay availability may be added.

7.2.3 Nanostring Analysis

From 3-5 FFPE slides RNA will be extracted using the Qiagen RNA/DNA FFPE kit and protocol. A Nanostring probeset including ca 20-800 immune and other marker related probes will be used using the Nanostring (Seattle) standard ordering and analysis process. The Nanostring nCounter available in the White lab at the University of Chicago will be used. Alternatively FFPE based RNAseq libraries may be constructed using the Illumina FFPE RNA access protocol. The lab is experienced with both the Nanostring and FFPE RNAseq process and additional details are available on request. These are exploratory analyses. Specific processing information will be made available in a continually updated SOP for tissue collection and processing.

7.2.4 Tumor DNA Analysis

Exome sequencing from tumor and normal blood white cells will be performed on the tumor samples for an exploratory analysis of correlation of genetic aberrations, immune phenotype and tumor response. In addition tumor RNAseq analysis will be performed from tumor tissue. Specific processing information will be made available in a continually updated SOP for tissue collection and processing.

7.2.5 Germline DNA analysis

Blood will be obtained from all patients for exome sequencing of normal DNA (see above). Specific processing information will be made available in a continually updated SOP for tissue collection and processing.

7.2.6 RNA analysis from blood

Blood samples will be obtained at baseline and after 3 weeks (administration of cycle 2 dose). Samples will be processed for RNA expraction (e.g. using thje PAXgene RNA kit/tubes). RNA will be analyses by Nanostring (see above) or RNAseq) in an exploratory fashion comparing baseline with on-treatment inflammatory markers. Specific processing information will be made available in a continually updated SOP for tissue collection and processing.

7.2.7 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below under Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 7.

Table 7 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	Total thriiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	Free tyroxine (T4)
Absolute Lymphocyte Count	*(CO_2 or biocarbonate)*	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Uric Acid		PK
	Calcium		
	Chloride		Blood for correlative studies
	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.

‡ If considered standard of care in your region.

Laboratory tests for screening or entry into the Second Course Phase should be performed within 10 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.2.6.1 Pharmacodynamic Evaluations

7.2.6.1.1 Blood Collection for RNA

Blood will be collected at baseline, and at the time of 2nd administration of pembrolizumab. Details are provided in the Flow Chart and a brief SOP for tissue will be available and updated continually during the study period containing specific details (tube color, numbers, HTRC contact info etc).

No Pharmacokinetic evaluations will be done.

7.2.7 Other Procedures

7.2.7.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events, which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. Subjects who a) attain a CR or b) complete 24 months of treatment with pembrolizumab may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 7.1.5.5. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.3.1) and then proceed to the Follow-Up Period of the study (described in Section 7.1.5.4).

7.2.7.2 Blinding/Unblinding

There is no blinding in this study.

7.2.8 Visit Requirements

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

7.2.8.1 Screening period

Screening period is 30 days prior to initiation of study drug. See flow chart under Section 6 for specific items.

- All patients must have completed curative intent therapy for locally advanced HNSCC within 24 weeks prior to enrollment.
- Tissue must have been collected **PRIOR** to starting curative intent therapy on all patients (see eligibility criteria)

7.2.8.2 Treatment Assignment

Cohort assignment will be based presence of acquired resistance versus suboptimal benefit as defined under study entry/inclusion criteria.

7.2.8.3 Treatment Period

Treatment period is 2 years or until progression.

7.2.8.4 Post-Treatment Visits

7.1.5.4.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial 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 90 days of the end of treatment 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 7.1.5.5) may have up to two safety follow-up visits, one after the Treatment Period and one after the Second Course Phase.

7.2.8.5 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 8-12 weeks (± 7 days) by radiologic imaging to monitor disease status. After 1 year, the imaging time point will occur every 12-16 weeks (± 7 days). 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 7.1.5.5. 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 7.1.5.5 will move from the follow-up phase to the Second Course Phase when they experience disease progression.

7.2.8.5.1 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 approximately every 12 to 16 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first OR at most 2 years out from the last patient receiving pembrolizumab.

7.2.8.6 Second Course Phase (Retreatment Period)

Subjects who stop pembrolizumab/epacadostat with SD or better may be eligible for up to one year of additional therapy with pembrolizumab + epacadostat 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 + epacadostat after attaining an investigator-determined confirmed CR according to RECIST 1.1, and
        - Were treated for at least 24 weeks with pembrolizumab + epacadostat before discontinuing therapy
        - Received at least two treatments with pembrolizumab and concurrent epacadostat (during that timeframe) beyond the date when the initial CR was declared

OR

    - Had SD, PR or CR and stopped pembrolizumab/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/epacadostat
- Did not receive any anti-cancer treatment since the last dose of pembrolizumab/epacadostat

- Has a performance status of 0 or 1 on the ECOG Performance Scale
- Demonstrates adequate organ function as detailed in Section 5.1.2
- Female subject of childbearing potential should have a negative serum or urine pregnancy test within 72 hours prior to receiving retreatment with study medication.
- Female subject of childbearing potential should be willing to use one of the following methods of contraception (*Intrauterine device (IUD), Vasectomy of a female subject's male partner, Contraceptive rod implanted into the skin*), 2 other methods of birth control (as listed in below footnote) or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 5.7.2). Subjects of child bearing potential are those who have not been surgically sterilized or have been free from menses for > 1 year.
- Male subject should agree to use an adequate method of contraception starting with the first dose of study 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 trial or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

Subjects who restart treatment will be retreated at the same dose and dose interval as when they last received pembrolizumab. Treatment will be administered for up to one additional year.

Footnote: two of the following contraception methods are acceptable when used in combination:
The two birth control methods can be 2 barrier methods or 1 barrier method plus 1 hormonal method to prevent pregnancy. The following birth control methods are allowed during the study:

- Barrier methods:
  - Diaphragm with spermicide (cannot be used with cervical cap
  - Cervical cap with spermicide (cannot be used with diaphragm)
  - Condom (male or female cannot be used together)
  - Copper intrauterine device (IUD)
  - Contraceptive sponge
- Hormonal methods:
  - Hormonal contraceptives (such as the birth control pill, skin patch, vaginal ring, or subcutaneous injection)

7.3 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any 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/Incyte products, is also an adverse event.

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

Merck/Incyte 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/Incyte for human use.

Adverse events may occur during the course of treatment in clinical trials or within the follow-up period specified by the protocol, or 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 adverse event unless it is considered to be drug related by the investigator.

All adverse events will be recorded from the time of first study drug administration through 90 days following cessation of treatment or if a subject initiates new anticancer therapy, whichever is earlier and at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1.

7.3.1 Definition of an Overdose for This Protocol and Reporting

For purposes of this trial, 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/Incyte 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/Incyte products 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 the Sponsor and within 2 working days hours to Incyte / Merck Global Safety as described below / in section 10.7.

7.3.2 Reporting of Pregnancy and Lactation

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial or within 120 days of completing the trial completing the trial, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All subjects and female partners of male subjects who become pregnant 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.

All Serious Adverse Events ("SAE"), including pregnancy and lactation exposure, required to be reported pursuant to the Protocol shall be provided to Incyte and its representatives by Institution or Principal Investigator within twenty-four (24) hours of learning of the event as well as any additional reports agreed upon by Institution or Principal Investigator and Incyte. SAE Reports will be sent to IncytePhVOpsIST@incyte.com. By sending to this e-mail address, the Incyte Pharmacovigilance group will receive copies of the reports. This process will be tested and established before the first patient is enrolled in the Study. Notwithstanding anything to the contrary herein, Institution will have the primary responsibility of reporting adverse events ("AE") to regulatory authorities."

Also see Section 10.7 for reporting to Merck Global Safety.

7.3.3 Immediate Reporting of Adverse Events to Incyte and Merck

7.3.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Merck/Incyte products that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is a new cancer (that is not a condition of the study);

- Is associated with an overdose;
- Is an other important medical event

Refer to Table 8 for additional details regarding each of the above criteria.

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 from the time of first dose of study drug through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to Merck/Incyte products, must be reported within 24 hours to the Sponsor and within 2 working days to Inctyte/Merck Global Safety as described in section 10.7.

Non-serious Events of Clinical Interest will be forwarded to Incyte / Merck Global Safety and will be handled in the same manner as SAEs.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Merck/Incyte products that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor and to Merck /Incyte as described in sectin 10.7.

This study will be conducted under an IND held by Dr. Alexander Pearson at the University of Chicago. Annual Progress Reports will be submitted as required by FDA. Additionally the IND holder will submit a copy of these reports to Incyte/Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215 993-1220) at the time of submission to FDA.

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

The investigator must assess and record the relationship of each SAE to the specific study drug, and report this as described in section 10.7. The original copy of the SAE Report and the fax confirmation sheet must be kept at the study site.

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable), and whether the patient continued or withdrew from study participation.

7.3.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest
(ECI) and must be reported within 24 hours to the PI as well as Incyte/Merck.

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

For the time period beginning at treatment allocation through 30 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to study products, must be reported within 24 hours.

Events of clinical interest for this trial include:

1. an overdose of one of the investigational products, as defined below under Definition of an Overdose for This Protocol and Reporting of Overdose, that is not associated with clinical symptoms or abnormal laboratory results.
2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

7.3.4 Evaluating Adverse Events

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

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

7.3.5 Definition of an Overdose for This Protocol and Reporting of Overdose

In this trial, an overdose is any dose higher than ≥1000 mg (5 times the dose) of pembrolizumab or ≥1000 mg of epacadostat. No specific information is available on the treatment of overdose of pembrolizumab or epacadostat. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is associated with ("results from") the overdose, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

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

All reports of overdose with and without an adverse event must be reported by the investigator within 24 hours to Incyte/Merck.

Table 8 Evaluating Adverse Events

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

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

	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Merck/Incyte products? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to investigational product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was the Merck/Incyte products 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 Merck/Incyte products; or (3) the trial is a single-dose drug trial); or (4) Merck/Incyte products(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Merck/Incyte products in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Merck/Incyte products(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE STUDY DRUG, APPROVAL FROM THE PI IS REQUIRED
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Merck/Incyte products or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Merck/Incyte products relationship).**	
Yes, there is a reasonable possibility of Merck/Incyte products relationship.	There is evidence of exposure to the Merck/Incyte products. The temporal sequence of the AE onset relative to the administration of the Merck/Incyte products is reasonable. The AE is more likely explained by the Merck/Incyte products than by another cause.	
No, there is not a reasonable possibility Merck/Incyte products relationship	Subject did not receive the Merck/Incyte products OR temporal sequence of the AE onset relative to administration of the Merck/Incyte products is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)	

7.3.6 Sponsor Responsibility for Reporting Adverse Events

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

7.4 Efficacy assessment

The primary study endpoint is **Response Rate** assessed per RECIST 1.1.

Disease progression (PD) will be evaluated by clinical and radiographic methods and date of progression will be recorded. Radiographic progression should be confirmed with a second scan 4-8 weeks after initial scan and treatment can continue until then.

If in question, disease progression should be confirmed pathologically. Site of disease progression will be classified as local (progression at primary tumor site), regional (progression in cervical lymph nodes), and/or distant (metastatic disease).

A diagnosis of second primary tumor must be confirmed pathologically. Deaths on study should be classified as disease (HNSCC), non-disease, or study treatment related.

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan

This study includes two cohorts. These will be handled as parallel cohorts/trials with the same statistical assumptions for both cohorts:

Primary Outcome: Response rate

Clinical and pathologic response rates will be determined and 90% confidence intervals obtained using the exact binomial distribution.

A Simon's two-stage design (Simon, 1989) will be used – using the Minimax variant - for both cohorts. The null hypothesis that the true response rate is 3% [p_0] (*assuming poor efficacy of e.g. pembrolizumab treatment in patients, who have failed prior PD-1/PD-L1 therapy*) will be tested against a one-sided alternative. In the first stage, 10 [n_1] patients will be accrued. If there are no responses [r_1] in these 10 [n_1] patients, the study will be stopped.

Otherwise, 5 additional patients will be accrued for a total of 15 [n] patients. The null hypothesis will be rejected if 2 or more responses are observed in 15 patients. This design yields a type I error rate of 0.0667 and 80% power when the true response rate is 20%.

A response rate of 20% would be considered clinically meaningful for HNC in the absence of alternative treatment options in the $2^{nd}/3^{rd}$ line setting (after PD-1/PD-L1 failure) and further development of pembrolizumab + epacadostat would proceed.

Secondary Outcome: Overall and Progression free survival / Safety

Survival: Assuming full enrollment of 30 patients, both cohorts will be combined for assessment of secondary outcome of one-year overall survival. Kaplan-Meier (1958) curves will be generated for overall (OS) and progression free survival (PFS); the latter endpoint will be defined as the time from enrollment until disease progression or death from any cause. Median OS and PFS will be estimated along with 90% confidence intervals using the method of Brookmeyer and Crowley (1982). Duration of response will be determined as the time from response until disease progression or death among the subset of patients who respond, and estimated by Kaplan-Meier. The disease control rate (CR+PR+SD) and 90% confidence interval will also be determined.

Toxicity: Toxicities will be summarized in tabular form by type and severity and incidence rates generated.

8.2 Sample Size

Sample size for each cohort is up to 15 patients (total of up to 30 patients).

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by Merck and Incyte and are summarized in Table 9.

Table 9 Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab 50 mg	Lyophilized Powder for Injection
Pembrolizumab 100 mg/ 4mL	Solution for Injection
Epacadostat tablets	25mg, 100mg

9.2 Packaging and Labeling Information

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

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

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

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

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

9.5 Returns and Reconciliation

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

Upon completion or termination of the study, all unused and/or partially used investigational product 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.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Food and Drug Administration (FDA) Approval

This study will be conducted under an IND held by Dr. Alexander Pearson at the University of Chicago. The University of Chicago CCTO will be responsible for facilitating all communications with the FDA on behalf of the IND holder. Participating sites should not communicate directly with the FDA.

10.2 New Protocol Distribution and IRB Submission

Once final Merck, Incyte, and University of Chicago (U of C) IRB approval is received, the protocol and consent form will be distributed via the Cancer Center website. This study is intended as a single center study to be run at the University of Chicago.

Before the study can be initiated the following documentation must be provided to the Cancer Clinical Trials Office (CCTO) at the University of Chicago Comprehensive Cancer Center.

- A copy of the official local IRB approval letter for the protocol and informed consent
- IRB membership list
- CVs and medical licensure for the principal investigator and any sub-investigators who will be involved in the study.
- Form FDA 1572 appropriately filled out and signed with appropriate documentation
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Investigational drug accountability standard operating procedures
- Additionally, before the study can be initiated at any site, the required executed research contract/subcontract must be on file with the University of Chicago.

10.3 Amendment Distribution and IRB Submission

All modifications to the protocol, consent form, and/or questionnaires will be submitted to the University of Chicago IRB for review and approval. A list of the proposed modifications or amendments to the protocol and/or an explanation of the need of these modifications will be submitted, along with a revised protocol incorporating the modifications. Only the Study Lead PI can authorize any modifications, amendments, or termination of the protocol. Once a protocol amendment has been approved by the University of Chicago IRB, the Regulatory Manager will send the amended protocol and consent form (if applicable) to the affiliate institutions electronically. Upon receipt of the packet the affiliate institution is expected to do the following:

- The affiliate must reply to the email from the Regulatory Manager indicating that the amendment was received by the institution and that it will be submitted to the local IRB.
- The amendment should be submitted to the affiliate institution's IRB as soon as possible after receipt. The amendment **must** be IRB approved by the institution **within 3 months** from the date that it was received.
- **The University of Chicago version date and/or amendment number must appear on the affiliate consent form and on the affiliate IRB approval letter.** The version dates can be found on the footer of every page of the protocol and consent form. The amendment number can be found on the University of Chicago IRB amendment approval letter that is sent with the protocol/amendment mailing.
- The IRB approval for the amendment and the amended consent form (if amended consent is necessary) for the affiliate institution must be sent to the designated UC Regulatory Manager as soon as it is received.

10.4 Annual IRB Renewals, Continuing Review and Final Reports

A continuing review of the protocol will be completed by the University of Chicago IRB and the affiliates' IRBs at least once a year for the duration of the study. The annual IRB renewals for the affiliate institution should be emailed promptly to the Regulatory Affairs Administrator. If the institution's IRB requires a new version of the consent form with the annual renewal the consent form should be included with the renewal letter.

10.5 Departure from the Protocol

An investigator cannot modify the protocol without satisfying procedures in this protocol as outlined in the study calendar. Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the study subject, must be reviewed and approved

by the local IRB. When a variation from the protocol is deemed necessary for an individual subject, the principal investigator or study chair must be contacted by phone or email (Alexander Pearson **, 773-834-1604 / 312-823-7990**, apearson@medicine.bsd.uchicago.edu). Such contact must be made as soon as possible to permit a decision as to whether or not the subject is to continue in the study.

The principal investigator or study chair must be informed of all intentional or unintentional departures from the protocol and will decide whether or not the subject is to continue in the study (Alexander Pearson**, 773-834-1604 / 312-823-7990**, apearson@medicine.bsd.uchicago.edu). All departures from the protocol, intentional and unintentional, along with the decision of the principal investigator will be submitted to the local and University of Chicago IRB per institutional guidelines.

10.6 Registration

Prior to registration and any study-specific evaluations being performed, all patients must have given written informed consent for the study and must have completed the pre-treatment evaluations. Patients must meet all of the eligibility requirements listed above. Study co-ordinators will register patients. This study is intended as a single center study performed at the University of Chicago.

When registering a subject, the following must occur:

- Confirm that a current IRB approval letter for the correct version of protocol/consent and has an annual update on file, if appropriate.
- Submit all required materials (Eligibility Checklist, Source documentation, & signed consent form) to confirm eligibility and required pre-study procedures to the CRA a minimum of 48 hours prior to the subject's scheduled therapy start date.
- Source documentation includes copies of all original documents that support each inclusion/exclusion criteria. The eligibility checklist does not serve as source documentation but rather as a checklist that original source documentation exists for each criterion.
- Communicate with the CRA to ensure all necessary supporting source documents are received and the potential subject is eligible to start treatment on schedule. If there are questions about eligibility, the CRA will discuss it with the PI. PI may clarify, but not overturn, eligibility criteria.
- Affiliate sites must confirm registration of subjects by obtaining a subject study ID number from the CRA via phone, fax or email.
- If a subject does not start on the scheduled day 1 treatment date, promptly inform the CRA as the delay in start may deem the subject ineligible and/or require further or repeat testing to ensure eligibility.

10.7 Reporting of Adverse Events to the Coordinating Center

Use the UC CCC protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

All serious adverse events (as defined above) and all adverse events that have been specified as Events of Special Interest occurring on this study require expedited reporting to the University of Chicago Comprehensive Cancer Center (UC CCC). The responsible Research Nurse or other designated individual at the treating site should report the SAE to the Study Lead Investigator, the University of Chicago CRA and the CCTO by the end of the business day when s/he becomes aware of the event. Events occurring after business hours should be reported to the CCTO by 12pm (noon) the next business day. Reports should be made using the 'Serious Event Report' or MedWatch 3500A Form.

UC CCC Cancer Clinical Trials Office Quality Assurance:
qaccto@bsd.uchicago.edu

Any serious adverse event, or follow up to a serious adverse event, whether or not related to Merck/Incyte products, must be reported within 2 working days of coordinating site awareness to Merck Global Safety. The coordinating site, the University of Chicago, will take responsibility for reporting the SAE to Merck/Incyte. Non-serious Events of Clinical Interest will be forwarded to Incyte/Merck Global Safety and will be handled in the same manner as SAEs.

1) **SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-993-1220.**

2) **All Serious Adverse Events ("SAE"), including pregnancy and lactation exposure, required to be reported pursuant to the Protocol shall be provided to Incyte and its representatives by Institution or Principal Investigator within twenty-four (24) hours of learning of the event as well as any additional reports agreed upon by Institution or Principal Investigator and Incyte. SAE Reports will be sent to IncytePhVOpsIST@incyte.com. By sending to this e-mail address, the Incyte Pharmacovigilance group will receive copies of the reports. This process will be tested and established before the first patient is enrolled in the Study. Notwithstanding anything to the contrary herein, Institution will have the primary responsibility of reporting adverse events ("AE") to regulatory authorities.**

An unexpected adverse event is are those not listed at the observed specificity or severity in the protocol, informed consent or IB. An unexpected adverse event is considered to be an unexpected adverse reaction if there evidence to suggest a causal relationship to the study agent. This may include a single occurrence of an event strongly associated with

drug exposure (e.g. Stevens-Johnson Syndrome), one or more occurrence of an event otherwise uncommon is the study population, or an aggregate analysis of specific events occurring at greater than expected frequency.

All unexpected adverse reactions must be reported to the IND holder so that the University of Chicago CCTO can inform the FDA. The responsible Research Nurse or other designated individual at the treating site should provide a complete written report using the FDA MedWatch 3500A form. The completed form should be sent to the CCTO at qaccto@bsd.uchicago.edu and to the Phase II CRA at PhaseIICRA@medicine.bsd.uchicago.edu within the specified timelines below regardless of whether all information regarding the event is available. If applicable, a follow-up report should be provided to the CCTO if additional information on the event becomes available.

Participating sites should not forward any adverse event reports directly to the FDA. The CCTO will report all events to the FDA as per the current FDA guidelines.

Fatal or Life-threatening Events: within 4 calendar days from treating investigator knowledge of the event

All Other Reportable Events: within 10 calendar days of treating investigator knowledge of the event

All serious adverse events should also be reported to the local IRB of record according to their policies and procedures.

10.8 Reporting of Adverse Events by the Coordinating Center

The designated UC CCC Regulatory Manager will notify all participating sites of all unexpected and serious adverse reactions that occur on this clinical trial and which are reported to the FDA and/or UC Institutional Review Board (IRB). When reported to the FDA, a copy of the completed Form 3500A (MedWatch) will be provided to the responsible Regulatory Manager by the CCTO IND Coordinator for distribution to all participating sites.

10.9 Data Management

Data reporting will be performed utilizing the eVelos electronic data capture system. The University of Chicago CRA will provide you with the applicable user registration information.

All required data must be recorded in the eVelos database at the completion of each cycle. AEs are to be entered in real time. SAEs are to be entered on the Serious Event Form within 24 hours of the site's knowledge of the event and sent via email (preferred) (accto@bsd.uchicago.edu; Fax: 773-702-4889). All case report forms must be completed by designated study personnel. Each screened (consented) patient is to be entered into eVelos within 48 hours of patient registration. In addition to direct data entry, you may be required

to provide supporting source documentation. Source records are original documents, data, and records (e.g., medical records, raw data collection forms, pharmacy dispensing records, recorded data from automated instruments, laboratory data) that are relevant to the clinical trial. Each site will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each subject enrolled in this clinical trial. Source records must be adequate to reconstruct all data transcribed onto the case report form.

10.10 Data and Safety Monitoring

This study will be remotely monitored by the designated University of Chicago Clinical Research Associate (CRA) in accordance with the University of Chicago, Section of Hematology/Oncology standard operating procedure titled Monitoring of Multi-Institutional Investigator Initiated Clinical Trials.

Prior to subject recruitment, and unless otherwise specified, a participating site will undergo a Site Initiation Teleconference to be conducted by the designated University of Chicago research team. The site's principal investigator and his or her study staff must attend the site initiation meeting.

Monitoring will be conducted to verify the following:

- Adherence to the protocol
- Completeness and accuracy of study data and samples collected
- Compliance with regulations
- Submission of required source documents

Participating sites will also undergo a site close-out teleconference upon completion, termination or cancellation of a study to ensure fulfillment of study obligations during the conduct of the study, and to ensure that the site Investigator is aware of his/her ongoing responsibilities.

Unless otherwise specified, this protocol will undergo weekly review at the multi-institutional data and safety monitoring teleconference as per procedures specified by the UC CCC NCI-approved Data and Safety Monitoring Plan. The conference will review:

- Enrollment rate relative to expectations, characteristics of participants
- Safety of study participants (Serious Adverse Event & Adverse Event reporting)
- Adherence to protocol (protocol deviations)
- Completeness, validity and integrity of study data

- Retention of study participants

Protocol deviations are to be documented using the Protocol Deviation. Deviations that are considered major because they impact subject safety or alter the risk/benefit ratio, compromise the integrity of the study data, and/or affect subjects' willingness to participate in the study must be reported within 7 days. Please contact the PI if you have questions about how to report deviations. All major protocol deviations should also be reported to the local IRB of record according to their policies and procedures

10.11 Auditing

A regulatory authority (e.g. FDA) may wish to conduct an inspection of the study, during its conduct or even after its completion. If an inspection has been requested by a regulatory authority, the site investigator must immediately inform the University of Chicago Cancer Clinical Trials Office and Regulatory Manager that such a request has been made.

10.12 Record Retention

Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

10.13 Obligations of Study Site Investigators

The Study Site Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Study Site Principal Investigator is responsible for personally overseeing the treatment of all study patients. He/she must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Study Site Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered into the CRFs. Periodically,

monitoring visits or audits will be conducted and he/she must provide access to original records to permit verification of proper entry of data.

11.0 APPENDICES

11.1 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.	

11.2 Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

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

11.3 RECIST 1.1 reference

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

* As published in the European Journal of Cancer:

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

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