Protocol Version 6.0 Dated February 15, 2018

SPONSOR: Georgetown University Medical Center
Georgetown Lombardi Comprehensive Cancer Center

TITLE: A phase II study of MK-3475 in patients with thymic carcinoma
Pembrolizumab (MK-3475) and Epacadostat (INCB024360) in thymic carcinomas

IND NUMBER: 125098/136867

Principal Investigator: Giuseppe Giaccone, MD PhD

Sub-investigators: Deepa Subramanian, MD, Stephen Liu, MD, Jillian Thompson NP

Pathology: Bhaskar Kallakury, MD, Jeoffrey Chahine, PhD

Statistician: Ming Tan, PhD

Biomarker Research: Yuwen Zhang, PhD

Affiliation: Georgetown University, Lombardi Comprehensive Cancer Center, Washington DC

Additional Institutions:

Co-Investigator (Affiliated Institution): Martin Gutierrez, MD

Affiliation: Hackensack University Medical Center, Hackensack N.J.

Co-Investigator: Gregory Riely

Affiliation: Memorial Sloan Kettering Cancer Center, New York

Drugs and Support provided by Merck and Incyte

1.0 TRIAL SUMMARY

Abbreviated Title	MK-3475 in thymic carcinomas
Trial Phase	II
Clinical Indication	Thymic carcinoma
Trial Type	Non-randomized
Type of control	Historical
Route of administration	IV
Trial Blinding	No
Treatment Groups	One treatment group only
Number of trial subjects	21-41
Estimated duration of trial	24 months
Duration of Participation	24 months

AMENDED TRIAL SUMMARY

Abbreviated Title	Pembrolizumab (MK-3475) and Epacadostat (INCB024360) in thymic carcinomas
Trial Phase	II
Clinical Indication	Thymic carcinoma
Trial Type	Non-randomized
Type of control	Historical
Route of administration	IV and PO
Trial Blinding	No
Treatment Groups	One treatment group only
Number of trial subjects	26
Estimated duration of trial	24 months
Duration of Participation	24 months

2.0 TRIAL DESIGN

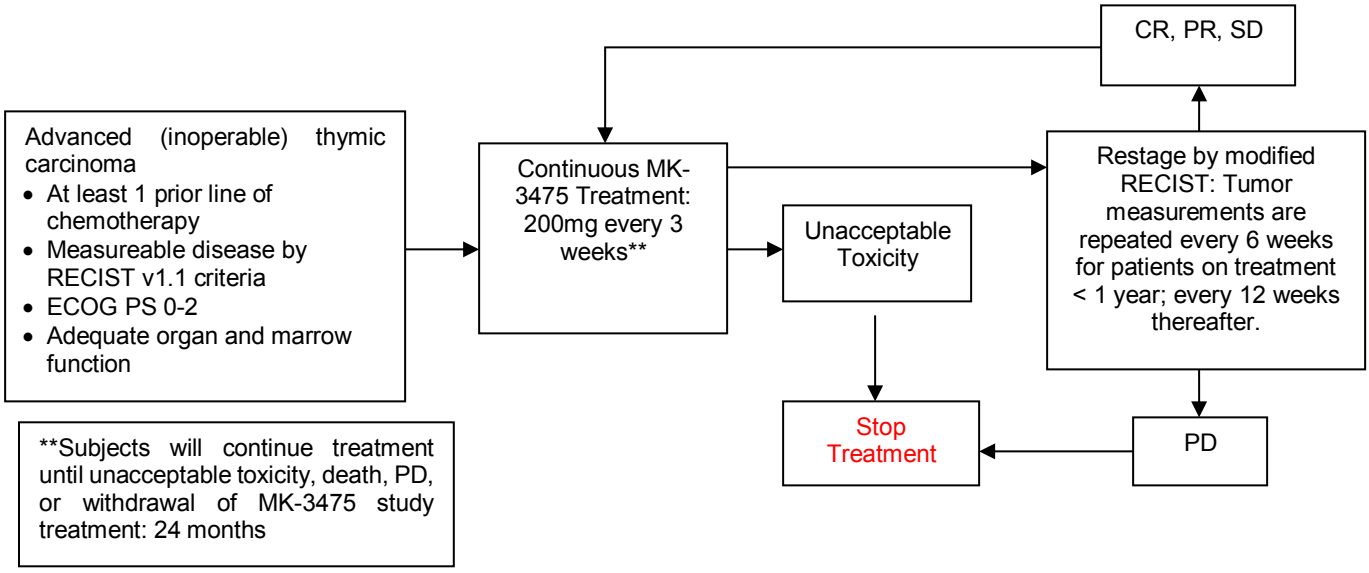
2.1 Trial Design

This is a phase II non-randomized clinical trial in patients with thymic carcinomas who failed prior systemic therapy.

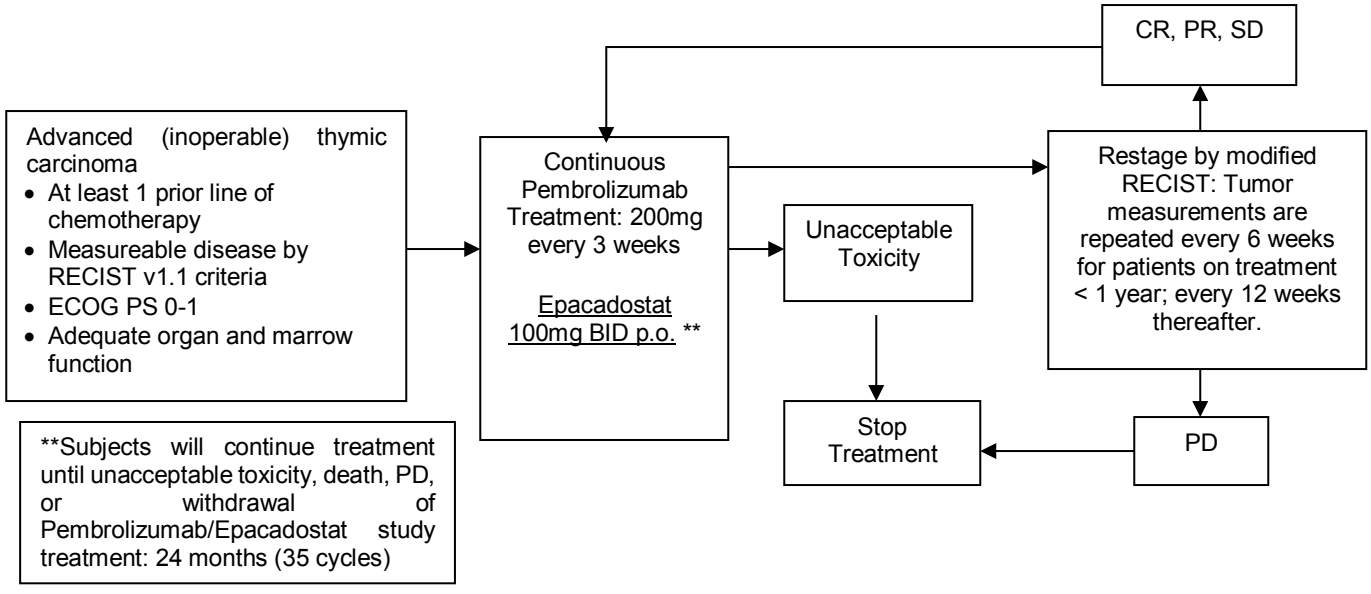
REASON FOR AMENDMENT

The results from 40 eligible patients treated with pembrolizumab showed enough evidence of activity to warrant further study in thymic carcinoma. The combination of pembrolizumab and epacadostat (an IDO1) inhibitor appears to have additive if not synergistic activity in preclinical models and very promising activity in advanced melanoma where sufficient information is available. A combination of pembrolizumab and epacadostat will be tested in an expansion cohort of this study in thymic carcinoma. Patients treated with pembrolizumab single agent will not be allowed.

2.2 Trial Diagram



AMENDED TRIAL DIAGRAM



3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

(1) **Objective:** Response Rate

Hypothesis: MK-3475 will determine a response rate of at least 20% in this rare tumor type

3.2 Secondary Objective(s) & Hypothesis(es)

(1) **Objective**: Progression-free survival, overall survival, tolerability

Hypothesis: MK-3475 will increase progression-free survival and overall survival compared to historical controls, and will be well tolerated.

3.3 Exploratory Objectives

(1) Correlate PDL-1 expression in tumor samples and outcome to treatment

(2) Develop conditionally reprogrammed cell from tumors whenever possible, in order to genetically characterize the tumor of origin

(3) Perform Next-generation sequencing on tumors and correlate the molecular profile with treatment outcome

3.0 AMENDED OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

(2) **Objective:** Response Rate

Hypothesis: Pembrolizumab (MK-3475) and Epacadostat (INCB024360) will determine a response rate of at least 45% in this rare tumor type

3.2 Secondary Objective(s) & Hypothesis(es)

(1) **Objective**: Progression-free survival, overall survival, tolerability

Hypothesis: Pembrolizumab (MK-3475) and Epacadostat (INCB024360) will increase progression-free survival and overall survival compared to historical controls (sunitinib or pembrolizumab single agent, see below), and will be well tolerated.

3.3 Exploratory Objectives

(1) Correlate PDL-1 expression in tumor samples and outcome to treatment

(2) Develop conditionally reprogrammed cell from tumors whenever possible, in order to genetically characterize the tumor of origin

(3) Perform Next-generation sequencing on tumors and correlate the molecular profile with treatment outcome

(4) Assess IDO1 expression in tumor samples and correlate it to treatment outcome

(5) Explore kynurein/tryptophan blood levels before and during treatment.

4.0 BACKGROUND & RATIONALE

4.1 Background

4.1.1 Pharmaceutical and Therapeutic Background for Pembrolizumab (MK-3475)

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [1]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various solid tumors. 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. Tumor-infiltrating lymphocytes can be expanded ex vivo and re-infused, inducing durable objective tumor responses in cancers such as melanoma [2; 3].

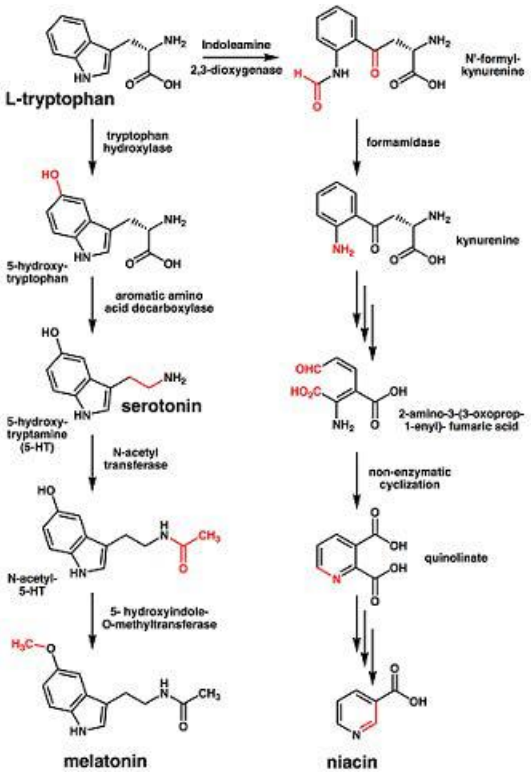
The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. 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) [4; 5]. The structure of murine PD-1 has been resolved [6]. 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 [5; 7; 8; 9]. 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 [10; 11]. 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 [12; 13]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells [14]. 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 [11; 15; 16; 17]. 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 [11]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. High expression of PD-L1 on tumor cells (and to a lesser extent of PD-L2) has been found to correlate with poor prognosis and survival in various cancer types, including renal cell cancer [18], pancreatic carcinoma [19], hepatocellular carcinoma [20], and ovarian carcinoma [21]. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma [22]. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

MK-3475 (previously known as SCH 900475) 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.

It is clear that whereas there are tumors that are very sensitive to PD-1 blockade, the majority of tumors are not and combinations with other strategies are warranted in order to increase efficacy. Combinations with other immunological agents is of particular interest. The CTLA4 and PD1 combination has been shown to be superior to PD1 and CTLA4 single agents in metastatic melanoma, however the combination has higher rates of severe toxicities.

4.1.2 IDO1 and Epacadostat (INCB024360), preclinical and clinical development Indoleamine 2,3-dioxygenase (IDO1) is a heme-containing monomeric oxidoreductase, which is expressed in tumor cells and antigen-presenting cells. IDO1 mediates catabolism of tryptophan (Trp) to kynurenine (Kyn) within immune cells and within a subset of tumor cells and increases local levels of cytotoxic tryptophan metabolites. See Figure below.



Tryptophan catabolism results in the inhibition of antitumor, cell-mediated immune responses through reduced cytotoxic and helper T-cell activities and increased regulatory (suppressor) T-cell activities.

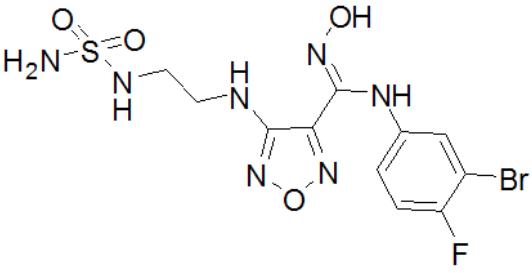
IDO1 is highly expressed in multiple tumor types, including melanoma, NSCLC, ovarian cancer, pancreatic cancer, colorectal cancer, glioblastoma, squamous cell carcinoma of the head and neck, endometrial carcinoma, DLBCL, renal cell cancer

and triple negative breast cancer. Accumulation of IDO1 expression in lymphnodes of melanoma patients was associated with decreased survival.

Epacadostat (INCB024360) is a potent, highly selective and orally available small molecule IDO1 inhibitor. In tumor-bearing mice, decreased Kyn levels (78%–87%) were observed in plasma, tumors, and lymph nodes.

In cell-based assays, epacadostat potently inhibits IDO1 in both human tumor cells and human dendritic cells (DCs) resulting in reduced Trp to Kyn conversion (IC50 values = 7.1-12.7 nM). Epacadostat does not significantly inhibit other proteins that could impact Trp catabolism.

The chemical name of epacadostat is (*Z*)-*N*-(3-bromo-4-fluorophenyl)-*N*′-hydroxy-4-(2-(sulfamoylamino)ethylamino)-1,2,5-oxadiazole-3-carboximidamide and the structural formula is presented in the Figure below. Epacadostat has a molecular formula of C11H13BrFN7O4S and a molecular weight of 438.23.



In preclinical models, IDO1-expressing tumors were sensitive to epacadostat monotherapy. IDO1 inhibition leads to increased number of TILs and decreased suppressor cells in tumors and enhanced IFN-γ secretion from TILs was observed following IDO1 inhibitor treatment.

A second gene, IDO2, was discovered that shares structural similarity (43% identity) to IDO1. Whereas human IDO1 can efficiently convert Trp to Kyn, human IDO2 does not do so effectively; therefore, the precise biological function of IDO2 is unclear.

Epacadostat did not produce any adverse effects after a single oral dose to rats (1000 mg/kg) in central nervous system (CNS) or respiratory safety pharmacology studies, and no adverse effects were noted in a cardiovascular study in telemeterized dogs. In repeat oral dose studies in mice, no adverse epacadostat-related effects were observed in any parameter evaluated. Clinical observations associated with epacadostat administration in the 3-month dog study included thin appearance and increased incidence of emesis and diarrhea (≥ 250 mg/kg per day) and lower food consumption and body weight loss (1000 mg/kg per day). Microscopic findings included lymphangiectasia in the small intestine (≥ 250 mg/kg per day), hepatocellular hypertrophy, lymphoid depletion of the thymus, and chronic inflammation with fibrosis and subacute inflammation in the large intestine (1000 mg/kg per day).

Combinations of epacadostat and checkpoint inhibition (both CTLA4 and PD-1 antibodies) were associated with enhanced T-cell proliferation and cytokine secretion in vivo. The combination of epacadostat and either an anti-mouse CTLA4 or an anti-mouse PDL1 antibody was also shown to act synergistically in significantly reducing tumor growth in a melanoma xenograft model.

Several clinical studies have been completed or are ongoing with epacadostat as single agent or in combination.

Study INCB 24360-101 was a completed Phase 1 with 52 patients. Subjects were administered doses of epacadostat ranging from 50 mg once daily (QD) to 700 mg BID. Fatigue was the most frequently reported TEAE (36 subjects, 69.2%). Two dose-limiting toxicities (DLTs) occurred; 1 DLT of radiation pneumonitis at the 300 mg BID dose level and 1 DLT of fatigue at the 400 mg BID dose level. A maximum tolerated dose (MTD) was not determined. Epacadostat plasma concentrations attained the peak values (Cmax) typically at 2 hours (median Tmax) postdose; the t½ was 2.9 hours. A high-fat meal did not cause a statistically significant change in epacadostat plasma exposures.

The clinical study ECHO-201 in untreated metastatic melanoma showed a response rate of 31% (vs 11% of historical control of ipilimumab) with the combination of ipilimumab and epacadostat. A large phase I followed by expansion cohorts (ECHO-202) in several tumor types has been performed with the combination of epacadostat and pembrolizumab. Out of 62 patients assessed in the phase I part, no excess toxicity was observed and no autoimmune disorders were noted. Out of 19 patients with melanoma 11 responded (58%). Based on these data a phase III study of this combination is ongoing in untreated melanoma (Gangadhar et al. ESMO 2016). In 12 advanced NSCLC there were 5 responders.

Five patients (8%) experienced treatment-related AEs that led to discontinuation, including grade 3 arthralgia, grade 3 AST increased/grade 2 ALT increased, grade 3 lipase increased, grade 3 aseptic meningitis, and grade 2 nervous system disorder. There were no treatment-related deaths. Table 1 below summarizes the treatment-related AEs.

Table1. **Related TEAEs ≥ 5% or Grade 3/4 TEAEs in ≥ 1 Subject in the Phase 1 Population in Study INCB 24360202**

Treatment-Related AEs,* n (%)	All Grades (n=62)	Grade 3/4 (n=62)	Treatment-Related AEs, n (%) cont'd	All Grades (n=62)	Grade 3/4 (n=62)
Total	**50 (81)**	**12 (19)**	Chills	5 (8)	0 (0)
Fatigue	18 (29)	0 (0)	Dizziness	5 (8)	0 (0)
Rash†	18 (29)	5 (8)	Myalgia	5 (8)	0 (0)
Pruritus‡	14 (23)	0 (0)	Constipation	4 (6)	0 (0)
Arthralgia	12 (19)	1 (2)	Headache	4 (6)	1 (2)
Diarrhea	11 (18)	0 (0)	Lipase increased	3 (5)	3 (5)
Nausea	10 (16)	1 (2)	Amylase increased	2 (3)	2 (3)
Pyrexia	7 (11)	0 (0)	Anxiety	2 (3)	1 (2)
Vomiting	7 (11)	1 (2)	Mucosal inflammation	2 (3)	1 (2)
AST increased	5 (8)	1 (2)	Meningitis aseptic	1 (2)	1 (2)

* All-grade AEs ≥5% or grade 3/4 AEs in ≥1 patient in total phase 1 population. † Rash includes the following MedDRA preferred terms: rash, rash erythematous, rash generalized, rash maculo-papular, rash pruritic, and rash follicular. ‡ Pruritus includes the following MedDRA preferred terms: pruritus and pruritus generalized.

Table 2: Summary of Treatment-Related Potential Immune-Related Adverse Events at 100 mg BID (Data Cutoff 28 MAR 2016)

Variable, n (%)	Epacadostat 100 mg BID (Phase 1)[a] (n = 18)	Epacadostat 100 mg BID (Phase 2)[b] (n = 99)
Rash[c]	0	13 (13.1)
Pruritus	0	4 (4.0)
Diarrhea	4 (22.2)	3 (3.0)
Arthralgia	4 (22.2)	3 (3.0)
Hypothyroidism	1 (5.6)	0
Adrenal insufficiency	0	0
Colitis	0	0
Pneumonitis	0	0

[a]In combination with pembrolizumab 2 mg/kg IV Q3W or 200 mg IV Q3W.
[b]In combination with pembrolizumab 200 mg IV Q3W.
[c]Rash includes the following terms: rash, rash generalized, rash macular, rash maculo-papular.

4.1.3 Preclinical and Clinical Trial Data

Refer to the Investigator's Brochures for Preclinical and Clinical data for both agents.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Thymic epithelial tumors (TET) are rare tumors of the thymic gland. There are approximately 400-600 new cases each year in the United States. Thymic carcinomas represent approximately 10% of the thymic malignancies, which are grossly divided into thymomas (WHO A – B) and thymic carcinoma (WHO C) [23]. Thymic carcinomas represent the most aggressive histological type among thymic malignancies. Survival depends on stage at presentation, histological features and completeness of resection when resectable. Many thymic carcinomas are unresectable and develop distant metastases. This is different from thymomas, especially the A subtype, which have about 100% survival at 10 years. The survival of thymic carcinomas is about 40% at 5 years. Another difference between thymomas and thymic carcinomas is that autoimmune syndromes, of which myasthenia gravis represents the most common one (30-40% in thymomas) are exclusively seen in thymomas but not in thymic carcinomas [24; 25; 26]. Of 17 patients tested for anti-cytokine autoantibodies, the majority of thymomas had one or more autoantibody present even if not associated to any autoimmune syndrome. In contrast, of 4 thymic carcinomas tested, only 1 had autoantibodies detectable in the blood [27]. In patients treated with cixutumumab (an antibody against IGF1R) 9/37 patients with thymoma developed an autoimmune syndrome but none (0/12) of the patients with thymic carcinomas, and patients with autoimmune syndromes had a worse survival [26]. Patient selection based on histology appears therefore very important.

Systemic treatment of patients with thymic epithelial tumors in advanced stage is chemotherapy. However chemotherapy induces responses in less than 50% of patients with thymic carcinomas. The classical PAC regimen (cisplatin, doxorubicin, cyclophosphamide) and more recently reported carboplatin and paclitaxel are among the more commonly utilized regimens [23; 28]. There is no standard treatment after failure of initial chemotherapy. I have conducted several phase II studies

in patients with TETs over the years and more recently with the use of targeted agents [29; 30; 31; 26; 32]. The most promising anticancer agent tested has been sunitinib, with a response rate of 26% (6/23) in patients with thymic carcinomas [32]. However tolerance has been suboptimal in this patient population.

Response rate in several phase II studies in thymic carcinomas ranged from 0% (several studies) to 26% with sunitinib (the highest response reported to date) [32]. Progression-free survival ranged from 1.7 [26] to 7.2 months [32].

There is an urgent need to develop active and well tolerated treatments for these patients.

Molecularly, thymic carcinomas are the most frequently mutated tumors among TETs with p53 mutations found in 26% of 47 cases that we analyzed using next generation sequencing [33]. The presence of frequent somatic mutations may make tumors more sensitive to blockade of immune check-points.

Expression of PDL-1 and PDL-2 has been demonstrated in normal cortical and medullary epithelial cells of the thymus from which thymic epithelial tumors derive. Importantly, 100% of invasive thymoma and 88% of thymic carcinomas were found positive for PD-L1 expression [15]. It is conceivable that presence of PDL-1 expression on thymic carcinoma cells might inhibit the immune system, similarly to what has been observed in several epithelial tumors.

PDL-1 is expressed on thymic stromal cells [34], and given the cellular relationship of normal thymus and thymic carcinoma, it is highly likely that thymic carcinoma is a prototypic disease for expression of PDL-1 and consequent limited success of therapy. We have a tissue bank and a tissue microarray of clinically annotated specimens from over 200 patients from which we can determine the incidence of PDL-1 expression. Approximately 100 are from thymic carcinomas. We intend to confirm the high level of expression as described before [15].

Recently a TMA study was presented [35] where 69 TETs and 17 normal thymic controls were included. Immunohistochemistry used a monoclonal antibody (clone 15, Sino Biological, Beijing, China) to human PD-L1 using human placenta for staining titration. To distinguish PD-L1 expression on epithelial cells from that on lymphocytes, a CK5/6 cytokeratin stain was used. The epithelial cells of both TETs and normal controls stained positive for PD-L1. All TETs had some level of positivity, however, PD-L1 staining intensity was significantly higher in TETs than controls. PD-L1 high TETs are more frequently of WHO subtype B2, B3, & C. PD-L1 high TETs was also associated with a worse prognosis (adjusted age/gender: OS, HR 5.4, p=0.035 and RFS HR 2.94, p=0.064). Three out of 4 tested thymic carcinomas displayed high PDL-1 expression.

The PD-1 pathway functions to limit unwanted or excessive immune responses, including autoimmune reactions. PD-L1 is typically expressed at low levels on various non-hematopoietic tissues, and PDL-2 is only detectably-expressed on antigen-presenting cells in the lymphoid tissue or chronic inflammatory environments. PDL-1 is also expressed in the tumor microenvironment of various cancers and activation of the PD-1 pathway may be a critical mechanism to evade T-cell mediated tumor rejection.

So far reports of autoimmune disease in patients treated with PD-1 or PDL-1 antibodies have been rare, however, given the propensity for some subtypes of thymomas to be associated with a broad range of auto-immune syndromes (myasthenia gravis being the most frequent), this study will only include patients with thymic carcinomas, which are not known to be associated with autoimmune syndromes.

Initial studies with PD-1 and PDL-1 antibodies have produced dramatic responses of significant duration in solid tumors traditionally known to be sensitive to immunotherapeutic approaches, such as renal cell carcinoma and melanoma, as well as epithelial tumors that are typically known to be refractory, such as non-small cell lung cancer. Pembrolizumab (MK-3475), a PD-1 antibody, has shown response rate of approximately 38% in patients with melanoma [36] and ~20% in patients with NSCLC. Pembrolizumab is presently approved for several solid tumors. Given the potential important role of the PD-1/PDL-1 axis in TETs, and the reportedly high level of expression of PDL-1 in these tumors, we completed a phase II study in thymic carcinoma using Pembrolizumab.

RATIONALE FOR THE AMENDMENT

The initial study of pembrolizumab alone recruited 41 patients with thymic carcinoma from March 2015 to December 2016 as a single institution at Georgetown University Medical Cancer. One patient was ineligible because of increased liver enzymes and received only one course of treatment. All the other patients are eligible. None had autoimmune disorders in their history or at start of treatment. Patient characteristics of the 40 eligible patients are listed in Table 3 below:

Table 3.

Patient characteristic	#
Gender: M/F	29/12
Median age (range), yrs	57 (25-80)
Race: Caucasian/African American/Latino/ Asian	33/2/1/4
Histology: squamous / thymic carcinoma unspecified / neuroendocrine / Castle	14/19/6/1
Stage: IVA/IVB	6/34
Performance status: 0/1/2	19/19/2

The treatment was in general well tolerated, and in line with the toxicity profile of pembrolizumab. However 6 patients developed autoimmune disorders: (1 myositis/myocarditis; 1 myositis/myocarditis/hepatitis/MG; 1 myositis/hepatitis; 1 bullous pemphigoid, 1 hepatitis; 1 hepatitis/pancreatitis/diabetes mellitus type 1). All autoimmune disorders were successfully treated with steroids, except the patient who developed diabetes. The two patients who developed myocarditis required pacemaker placing. Five patients developed hypothyroidism and one hyperthyroidism. The only factor that was significantly associated with risk of developing a severe autoimmune disorder was female gender (4/6; p=.026).

As of January 2017, all 40 eligible patients had at least one restaging assessment and the response rate is 22.5%: 1 complete response, 8 partial responses (plus 1 unconfirmed), 20 patients with stable disease and 11 progressions. Two partial responses show minimal residual disease and negative PET scans. Two responders have progressed and 5 responses are beyond 12 months duration.

Of 29 cases where PD-L1 staining was tested (Dako 22C3), high PD-L1 ($\geq$50% tumor cells positive) was found in 8 cases (28%); of the 9 responders 6 had high PD-L1 expression. Targeted next generation sequencing performed so far in 15 cases did not show correlation between mutational burden and response.

Further assessment of PD-L1 and completion of NGS are underway, as well as Nanostring.

Given the relatively high response rate, similar to other tumors where pembrolizumab is active (e.g. lung cancer), and the long duration of responses, despite the onset of newly diagnosed autoimmune disorders, it is felt that an attempt should be made to try and increase the response rate even further by combining pembrolizumab with the IDO inhibitor Epacadostat (INCB024360). The addition of Epacadostat to pembrolizumab has led to an increase in the response rate in melanoma and non-small cell lung cancer (ASCO 2017) and an attempt to increase the response rate in patients with thymic carcinoma beyond that of pembrolizumab single agent is warranted.

4.2.2 Rationale for Dose Selection/Regimen/Modification

Pembrolizumab

An open-label Phase I trial (Protocol 001) was conducted to evaluate the safety and clinical activity of single agent Pembrolizumab. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of Pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. 10.0 mg/kg Q2W, the highest dose tested in PN001, will be the dose and schedule utilized in Cohorts A, B, C and D of this protocol to test for initial tumor activity. Recent data from other clinical studies within the Pembrolizumab program has shown that a lower dose of Pembrolizumab and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of Pembrolizumab administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing a Q2W and Q3W dosing schedule.

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of Pembrolizumab were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. Pembrolizumab has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for Pembrolizumab in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

Pembrolizumab in combination with epacadostat

The safety profile for the 300mg bid dose of epacadostat in combination with pembrolizumab in the Phase I/II study (INCB24360-202) did not exceed the MTD. 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 most of current protocols of this combination.

The dose combination of 100 mg bid epacadostat plus pembrolizumab for the ongoing 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, greater target coverage for inhibition of IDO1 may be necessary. PK/PD modelling suggests that doses of 100mg bid epacadostat achieve an average IC50 at trough in most patients. At 300mg bid, epacadostat achieves target inhibition above the IC90 at trough. Greater target inhibition may be necessary in more resistant tumors, and potentially balances benefit/risk in favor of the higher epacadostat dose combination given that the dose does not exceed the MTD.

In the present study a dose of epacadostat of 100mg BID has been selected, based on the fact that pembrolizumab had activity in our previous cohort of pembrolizumab as single agent, and based on a potentially lower side effect profile.

4.2.3 Rationale for Endpoints

Given the rarity of the disease, and the relatively indolent natural course, response rate will be the primary endpoint of this study.

4.2.3.1 Efficacy Endpoints

Response rate is the primary endpoint.

Secondary endpoints: progression-free survival, overall survival and tolerability.

4.2.3.2 Biomarker Research

Archival tissue or a new biopsy will be used to perform immunohistochemistry for PDL-1 staining. PDL-1 expression and response to treatment will be correlated.

Whenever feasible fresh tissue will be obtained to establish new cell lines, using the recently established method of "conditionally reprogrammed cells" [37]. Cells will be characterized with several immunohistochemistry markers and a genetic level (see below).

Tumor tissues (either fresh and paraffin embedded) will be submitted to Next-Generation sequencing for a selected number of genes [33; 38]. Correlation between number and type of mutations and response to treatment will be studied. Results obtained in new biopsies will be compared to those obtained before systemic treatment, since potentially this could increase or change the mutational spectrum of the tumor.

In patients where a new biopsy will be available, PDL-1 expression will be performed and compared to the archival material, since potentially exposure to systemic treatment might change the expression of this immune check-point. Expression of IDO1 will also be assessed as an exploratory study in tumor samples.

1. **Correlation between PD-L1 expression in thymic carcinomas and response to anti-PD-1 antibody therapy**. **Immunohistochemistry Procedure:** The anti-PD-L1, 22C3 antibody which is an FDA approved Ready-to-Use Kit (SK006), will be used for PD-L1 staining, The expected staining pattern (based on literature) is membranous staining. **Specimen preparation:** The antibody can be used for labeling formalin-fixed, paraffin-embedded tissue sections and cytology cell blocks. Tissue specimens should be cut into sections of approximately 4 µm. Pre-treatment of formalin-fixed, paraffin-embedded tissue sections with heat-induced epitope retrieval (HIER) is required. Optimal results are obtained by pretreating tissues with HIER using diluted Envision FLEX Target Retrieval Solution, **Low pH (50x)** (K8004). Deparaffinization, rehydration and epitope retrieval are performed in DAKO PT Link (PT100/PT101). The following parameters are used for PT Link: **Pre-Heat temperature: 65ºC, epitope retrieval temperature and time: 97ºC for 20 minutes, cool down to 65ºC.** Racks are placed in diluted Envision Flex Wash Buffer (20x) (code K8007) for 5 minutes. The slides are first incubated with Envision Flex Peroxidase-Blocking reagent (Cat# K8002-SM801), followed by the primary antibody Anti-PD-L1. Then an incubation with a secondary antibody Envision Flex Rabbit Linker

(Cat# K8002-SM805) is followed by the HRP (labeled polymer) (Cat#K8002-SM802), and the staining procedure is finalized with the addition of Envision Flex DAB+ chromogen + substrate buffer solution (Cat# K8002-SM803). The stained slides are evaluated by a pathologist to confirm staining specificity as well as tumor cells positive percentage and intensity. Tumor cells percentage positive and intensity will be retrospectively correlated to response to treatment.

2. **Correlation between the type/number of genetic mutations of thymic carcinomas and PD-L1 expression as well as response to anti-PD-1 antibody therapy:** Our whole exome and targeted cancer-associated gene sequencing studies [33; 38] revealed that thymic carcinomas exhibit higher incidence of somatic non-synonymous mutations than thymomas. In addition to the previously reported TP53 and KIT mutations, epigenetic regulatory genes were also found recurrently mutated in thymic carcinomas but not in thymomas. Preliminary data have suggested that heavy smokers who accumulate many somatic mutations in NSCLCs may be more sensitive to PD-L1 and PD-1 antibody therapies (Soria JC, ECC, 2013, Amsterdam). We hypothesize that additional mutations may appear after chemotherapy that could potentially lead to PD-L1 upregulation in thymic carcinomas and therefore induce sensitivity to PD-1 antibody therapy. Thus we plan to explore whether specific genetic mutations and the number of mutations are associated with PD-L1 expression in thymic carcinomas and patients' response to PD-1 therapy. Attempts will be made to obtain tumor material before enrolling onto this study. Samples (fresh or FFPE samples) collected post chemotherapy and their normal blood pairs as well as 10 fresh or archived FFPE tumor materials derived from the same patients before systemic chemotherapy will be sequenced using NEXTGEN technology on our recently acquired Miseq sequencer in the lab. A custom-designed cancer-associated gene (~220) panel which includes all the identified recurrent mutations in thymic carcinomas [33; 38], published cancer driver genes [39] and COSMIC cancer gene census (http://cancer.sanger.ac.uk/cosmic/census) has been used for targeted sequencing. Comparative sequencing analysis of the tumor/blood pairs allows us to identify specific somatic mutations and the number of somatic mutations in a given tumor. Moreover, comparative analysis of tumor samples from the same patient before and after systemic treatment can uncover whether the tumor may acquire additional mutations after chemotherapy. The data will be employed to evaluate the correlation between the type/number of mutations and PD-L1 expression in the tumors and patients' response to PD-1 antibody therapy. So far we have analyzed 15 samples from the Pembrolizumab phase II study, and there does not seem to be a direct relation between tumor burden or specific mutations and response. Further analysis will be performed on the rest of the samples.

   There is new data suggesting that mutational burden and the use of whole exome sequencing may allow the identification of neoepitopes (Rizvi et al. Science 2015). In the next cohort of pembrolizumab and Epacadostat, we will perform whole exome sequencing. This will be done by contracting an outside sequencing facility (to be determined).

3. **The impact of genetic heterogeneity of thymic carcinomas on the response to anti-PD-1 antibody therapy**: Whenever the fresh tumors are available, we plan to establish cell

lines or grow the primary tumor cells in culture using the "Conditional Cell Programming" technology recently described by Dr. D. Schlegel of our institute [37]. This new technology has allowed us to establish several cell lines from thymic epithelial tumors. During the course of this study, we observed that some thymic carcinomas of the same patients formed morphologically distinguishable colonies in vitro and some didn't. It is possible that the morphologically distinguishable colonies may be derived from subclones of an individual tumor. Tumor heterogeneity is thought to be a significant challenge to single-agent targeted therapy and to be an inevitable resistant mechanism to targeted therapy. Whether tumor heterogeneity may have an impact on PD-1 antibody therapy remains unclear. Fresh tumor specimens will be propagated in culture. Morphologically distinguishable or similar colonies derived from individual tumors will be expanded and isolated for NEXTGEN sequencing as described above. Somatic mutations will be compared among the same tumor-derived colonies and tumor heterogeneity will be determined based on the genomic mutation information. Individual tumor-derived colonies will be examined for PD-L1 expression and thymic carcinoma-related immunological markers (cytokeratins, C-Kit, E-Cad, EpCam, P63 etc) by immunofluorescence analysis. The results will be compared with PD-L1 expression of primary tumors and patients' response to PD-1 antibody therapy. The study will enable us to determine the effectiveness of PD-1 antibody therapy on thymic carcinomas in relation to their tumor heterogeneity status.

Fresh material and archival material should be sent to:

Yuwen Zhang, PhD in Giaccone's Laboratory,

Lombardi Comprehensive Cancer Center, Georgetown University, Research Bldg., room E212, 3970 Reservoir Rd., Washington DC 20007, tel 202 6874738.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Patients with advanced thymic carcinoma, for whom no radical treatment exists, who have failed at least one line of prior chemotherapy.

5.1.2 Subject Inclusion Criteria

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

1. Histologic confirmation of thymic carcinoma (WHO Classification, See Appendix 12.1)

2. Advanced disease (Masaoka staging, See Appendix 12.2) not amenable to curative treatment.

3. At least 1 prior line of chemotherapy.

4. Progression of disease must be documented prior to study entry.

5. Absence of any autoimmune syndrome typically associated with thymomas but not thymic carcinomas (myasthenia gravis, pure red cell aplasia, etc.).

6. Be willing and able to provide written informed consent/assent for the trial.

7. Be ≥ 18 years of age on day of signing informed consent.

8. Have measurable disease based on RECIST 1.1.

9. Have provided tissue from an archival tissue sample or newly obtained core or excisional biopsy of a tumor lesion.

10. Have a performance status of 0 or 1 on the ECOG Performance Scale (See Appendix 12.3).

11. Demonstrate adequate organ function as defined in Table 4, all screening labs should be performed within 10 days of treatment initiation.

Table 4. 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
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** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) 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 ≤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.	

12. Female subject of childbearing potential should have a negative urine or serum pregnancy 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.

13. 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.

14. 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. Has disease which is amenable to radical treatment with surgery or radiation or a combination of treatments.

2. Is currently participating in or has participated in a study of an investigational agent or using an investigational device within 4 weeks of the first dose of treatment.

3. 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.

4. Has had a prior monoclonal antibody within 4 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.

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

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

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

6. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.

7. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment.

8. Has an active automimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjorgen's syndrome will not be excluded from the study.

9. Has evidence of interstitial lung disease

10. Has a history of non-infectious pneumonitis that required steroids, or has a history of active pneumonitis.

11. Has an active infection requiring systemic therapy.

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 hypersensitivity to pembrolizumab (MK-3475) or its formulation.

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

15. 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.

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

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

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

19. Has received a live vaccine within 30 days prior to the first dose of trial treatment.

20. Inability to swallow food or any condition of the upper gastrointestinal tract that precludes administration of oral medications.

21. Screening ECG with QTc interval > 480 milliseconds (corrected by Fridericia). In the event that a single QTc is >480 msec, the subject may enroll if the average QTc for 3 ECGs is < 480 msec.

22. Prior receipt of an IDO inhibitor.

23. Receipt of MAOIs within 21 days before first dose of study treatment.

24. History of serotonergic syndrome.

5.2 Trial Treatments

The treatment to be used in this trial is outlined below in Table 5

Table 5. Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	200 mg flat dose	Every 3 weeks	IV infusion	3 weeks	Experimental
Epacadostat	100 mg BID	Daily	PO	3 weeks	Experimental
Dose and interval modifications of Epacadostat can be found in Section 5.2.1.2.					

Trial treatment should begin within a week from registration into the trial.

5.2.1 Dose Selection/Modification

5.2.1.1 Pembrolizumab

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

Dose Modifications

Pembrolizumab will be withheld for drug-related Grade 4 hematologic toxicities, non-hematological toxicity ≥ Grade 3 including laboratory abnormalities, and severe or life-threatening AEs as per Table 6. There are no dose modifications for pembrolizumab.

Table 6. Dose modification guidelines for drug-related adverse events.

Toxicity	Grade	Hold Treatment (Y/N)	Timing for restarting treatment	Dose/Schedule for restarting treatment		Discontinue Subject (after consultation with PI)
				Epacadostat	Pembrolizumab	
Hematological Toxicity	1, 2	No	N/A	N/A	N/A	N/A
	3	Yes	Toxicity resolves to Grade 0-1 or baseline	N/A		Toxicity does not resolve within 6 weeks of last infusion *Permanent discontinuation should be considered for any severe or life-threatening event*
	4	Yes	Toxicity resolves to Grade 0-1 or baseline	Reduce dose by one dose level	. Restart for following events: grade 4 neutropenia for ≤ 7 days, grade 4 lymphopenia or leukopenia; for all other Grade 4 hematological toxicity pembrolizumab may not be restarted	
Non-hematological toxicity Note: Exception to be treated similar to grade 1 toxicity • Grade 2 alopecia • Grade 2 fatigue For additional information regarding Adverse Events with a potential Immune-Etiology reference Section 5.6.1.1.	1	No	N/A	N/A	N/A	N/A
	2	Consider withholding for persistent symptoms	Toxicity resolves to Grade 0-1 or baseline	Restart at the same dose	*Clinical AE resolves within 4 weeks*: Same dose and schedule *Clinical AE does not resolve within 4 weeks:*	Toxicity does not resolve within 12 weeks of last infusion
	3	Yes	Toxicity resolves to Grade 0-1 or baseline	Restart at 1 dose level lower		Toxicity does not resolve within 6 weeks of last infusion; *Permanent discontinuation should be considered for any severe or life-threatening event*
	4	Yes	Toxicity resolves to Grade 0-1 or baseline	Restart at 1 dose level lower	Restart only permitted as noted b. For all other Grade 4 non-hematological toxicities, pembrolizumab may not be restarted	Toxicity does not resolve within 6 weeks of last infusion; *Permanent discontinuation should be considered for any severe or life-threatening event*

Note: Subjects who experience a recurrence of the same severe or life-threatening AE at the same grade or greater treatment should be discontinued from study treatment.

a) The following exceptions for asymptomatic amylase or lipase do not require a dose delay: Grade 3 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis. It is recommended to consult with the medical monitor for Grade 3 amylase or lipase abnormalities.

b) Isolated Grade 4 lipase or amylase abnormalities not associated with symptoms or clinical manifestations of pancreatitis. Medical monitor should be consulted for any Grade 4 amylase or lipase abnormality.

In case toxicity does not resolve to Grade 0-1 within 6 weeks after last infusion, treatment should be discontinued after consultation with the PI. With treating investigator and PI agreement, subjects with a laboratory adverse event still at Grade 2 after 12 weeks may continue treatment in the trial only if asymptomatic and controlled. For information on the management of adverse events, see Section 5.6.1.

Subjects who experience a recurrence of the same severe or life-threatening event at the same grade or greater with re-challenge of Pembrolizumab should be discontinued from trial treatment.

5.2.1.2 Epacadostat

Description and Administration

Epacadostat will be available as 25 or 100 mg tablets to be administered in a BID administration schedule. All BID doses of epacadostat will be taken PO in the morning and evening, approximately 12 hours apart without regard to food. If the morning or evening dose is missed by more than 4 hours, then that dose should be skipped, and the next scheduled dose should be taken at the usual time. Doses of epacadostat will be self-administered except on the days scheduled to be given at the study clinic.

Subjects should be counseled by the investigator to maintain strict adherence to the study regimen as prescribed and to keep a record of any missed doses. The subject will be instructed to bring all unopened, empty, and opened/partially used bottles of study drug at Day 1 study visits, at which time compliance will be assessed.

Supply, Packaging, and Labeling

Study drug tablets are packaged in high-density polyethylene bottles; no preparation is required.

Storage

Bottles should be stored at room temperature, 15°C to 30°C (59°F to 86°F) and closed tightly to protect the tablets from humidity.

Instruction to Subjects for Handling Epacadostat

The subject must be instructed in the handling of study drug as follows:

- To store the study drug at room temperature.
- To only remove from the study drug bottle/kit the number of tablets needed at the time of administration.
- Not to remove doses in advance of the next scheduled administration.
- To make every effort to take doses on schedule.
- To report any missed doses.
- If the subject vomits after taking study drug, the subject should not take another dose.

- If the morning or evening dose of epacadostat is missed by more than 4 hours, then that dose should be skipped, and the next scheduled dose should be taken at the usual time.
- To keep study drug in a safe place and out of reach and sight of children.
- To bring all used and unused study drug kits to the site at each visit.

Epacadostat Dose Modifications

Table 7 describes epacadostat dose reductions that may occur due to any related AEs. Dose reductions should occur in a step-wise fashion from the initial starting dose of the cohort, and a maximum of 1 dose reduction of epacadostat is allowed for the management of an AE, regardless of the initial starting dose. If an AE recurs/does not return to baseline after the second dose reduction of epacadostat, then the subject must permanently discontinue epacadostat. If a subject does not tolerate 50 mg BID, then the subject must permanently discontinue epacadostat.

Table 7: Epacadostat Dose Reductions

Dose Level	Dose
0	100 mg BID
-1	50 mg BID

5.2.2 Timing of Dose Administration

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

5.2.3 Timing of Dose Administration (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, then that dose should be skipped, and the next dose should be taken at the next scheduled time point. 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, with the first dose administered in the evening 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 Day 1 of each cycle in the clinic. 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.

5.2.4 Trial Blinding/Masking

This is an open-label trial; therefore, there will be no blinding or masking.

5.3 Randomization or Treatment Allocation

This is a single arm non-randomized phase II study.

5.4 Stratification

There is no stratification for this study.

5.5 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The treating 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. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the treating Investigator, the PI, and the subject.

5.5.1 Acceptable Concomitant Medications

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

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2.

5.5.2 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, unless otherwise noted below:

- Anti-cancer systemic chemotherapy or biological therapy

- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Use of any MAOI or drug associated with significant MAOI activity agents is prohibited from 21 days prior to Day 1 through 2 weeks after the final dose of epacadostat has been administered
- Investigational agents other than Pembrolizumab and Epacadostat
- Radiation therapy

  Note: In the presence of a mixed response (some lesions improving or stable and other lesions progressing), radiation therapy to a symptomatic solitary lesion or to the brain is allowed.
- Administration of a live attenuated vaccine within 30 days before the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.
- Any chronic immunological-suppressive treatment for any reason. (**Note:** Inhaled or topical steroids are allowed, and systemic steroids at doses ≤10 mg/day prednisone or equivalents are allowed and immune suppressants are allowed for short-term treatment for immune toxicities or as prophylaxis for contrast allergy for imaging procedures)
- Use of any immunological-based treatment for any reason from screening through follow-up visit is prohibited.

  Note: Completed adjuvant therapy (eg, vaccines) with medical monitor approval, inhaled or topical steroids, and systemic steroids at doses ≤ 10 mg/day prednisone equivalents are allowed, as described in Restricted Medications.
- 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 supplements, mefenamic acid, mycophenolic acid, niflumic acid, nilotinib, phenobarbital, phenylbutazone, phenytoin, probenecid propofol, quinidine, ritonavir, sorafenib, sulfinpyrazone, valproic acid, and verapamil.

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

The Exclusion Criteria describes other medications which are prohibited in this trial.

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

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines

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

- Nausea/vomiting: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Subjects should be strongly encouraged to maintain liberal oral fluid intake.

- Anti-infectives: Subjects with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.

- Immune-related adverse events: Please see Section 5.6.1.1 below and the separate guidance document in the administrative binder regarding diagnosis and management of adverse experiences of a potential immunologic etiology.

- Management of Infusion Reactions: Acute infusion reactions (which can include cytokine release syndrome, angioedema, or anaphylaxis) are different from allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Signs/symptoms may include: Allergic reaction/hypersensitivity (including drug fever); Arthralgia (joint pain); Bronchospasm; Cough; Dizziness; Dyspnea (shortness of breath); Fatigue (asthenia, lethargy, malaise); Headache; Hypertension; Hypotension; Myalgia (muscle pain); Nausea; Pruritis/itching; Rash/desquamation; Rigors/chills; Sweating (diaphoresis); Tachycardia; Tumor pain (onset or exacerbation of tumor pain due to treatment); Urticaria (hives, welts, wheals); Vomiting.

Table 8 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of Pembrolizumab.

Table 8. 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	**Stop Infusion and monitor symptoms.**	

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	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 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. For Further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov and Appendix		

5.6.1.1 Supportive Care Guidelines for Events of Clinical Interest and Immune-related Adverse Events (irAEs)

Events of clinical interest of a potential immunologic etiology (irECIs) may be defined as an adverse event of unknown etiology, associated with drug exposure and is consistent with an immune phenomenon.

This section is meant to apply to suspected irAEs from epacadostat, pembrolizumab, or the combination. Immune-related AEs may be predicted based on the nature of the pembrolizumab or epacadostat compounds, their mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. Special attention should be paid to AEs that may be suggestive of potential irAEs. An irAE can occur shortly after the first dose or several months after the last dose of treatment.

General recommendations to managing irAEs not detailed elsewhere in the Protocol are detailed in Table 9 Recommendations for management of specific immune-mediated AEs such as pneumonitis, enterocolitis, hepatitis, dermatitis, neuropathies, endocrinopathies, and other immune-mediated AEs are detailed in the sections below.

An irAE can occur shortly after the first dose or several months after the last dose of treatment. If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an adverse event as an irAE. Subjects who develop a Grade 2 or higher irAE should be discussed immediately with the PI. Recommendations to managing irAEs not detailed elsewhere in the protocol are detailed in Table 9.

Table 9. **General Approach to Handling Immune-Related Adverse Events**

irAE	Withhold/Discontinue Pembrolizumab and Epacadostat	Guidance for Restarting Study Treatment	Supportive Care
Grade 1	No action.	Not applicable.	Provide symptomatic treatment.
Grade 2	May withhold pembrolizumab and epacadostat per investigator's discretion.	May return to treatment if improves to Grade 1 or resolves within 6 weeks. If AE resolves within 4 weeks, subject may restart at the same dose and schedule for both pembrolizumab and epacadostat. For an AE that does not resolve within 4 weeks, epacadostat should be reduced 1 dose level, but pembrolizumab may be restarted at the same dose and schedule. If AE does not resolve within 6 weeks, study treatment with both study drugs should be discontinued or discussed with medical monitor.	Consider systemic corticosteroids in addition to appropriate symptomatic treatment.
Grade 3	Withhold or discontinue pembrolizumab and epacadostat. Discontinue if unable to reduce corticosteroid dose to < 10 mg/day of prednisone or equivalent within 6 weeks of toxicity.	Any restart of study treatment must be discussed with medical monitor before restarting treatment.	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. May use 1 to 2 mg/kg of prednisone or equivalent per day. Steroid taper should be considered once symptoms improve to ≤ Grade 1 and tapered over at least 4 weeks in most cases.
Grade 4	Discontinue pembrolizumab and epacadostat.	Not applicable. Any exceptions require medical monitor approval.	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. May use 1 to 2 mg/kg of prednisone or equivalent per day.

5.6.1.2 Supportive Care Guidelines for Pneumonitis

Subjects with symptomatic pneumonitis should immediately stop receiving Pembrolizumab and Eapacadostat and have an evaluation. The evaluation may include bronchoscopy and pulmonary

function tests to rule out other causes such as infection. If the subject is determined to have study drug associated pneumonitis, the suggested treatment plan is detailed in Table 10.

Table 10. Recommended Approach for Handling Noninfectious Pneumonitis

Study Drug(s) Associated Pneumonitis	Withhold/Discontinue Pembrolizumab and Epacadostat	Guidance for Restarting Study Treatment	Supportive Care
Grade 1 (asymptomatic)	No action.	Not applicable.	Intervention not indicated.
Grade 2	Withhold pembrolizumab and epacadostat.	**First episode of pneumonitis:** If improves to near baseline: Decrease the dose of epacadostat by 1 dose level, and for pembrolizumab, restart at same dose and schedule subsequent cycles. If not improved after 2 weeks or worsening, permanently discontinue pembrolizumab. Discuss with medical monitor if restart with epacadostat is permitted. **Second episode of pneumonitis:** Permanently discontinue pembrolizumab and epacadostat if upon rechallenge subject develops pneumonitis ≥ Grade 2.	Systemic corticosteroids are indicated. Taper if necessary.
Grades 3 and 4	Discontinue pembrolizumab and epacadostat.	Not applicable. Any exceptions require medical monitor approval.	Systemic corticosteroids are indicated. The use of infliximab may be indicated as appropriate.

5.6.1.3 Procedures and Guidance for Enterocolitis

Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, mucus or blood in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic subjects, infectious etiologies should be ruled out, and endoscopic evaluation should be considered for persistent or severe symptoms. Recommendations for management of enterocolitis are shown in Table 11.

Table 11. Recommended Approach for Handling Enterocolitis

Study Drug(s) Associated Enterocolitis	Withhold/Discontinue Pembrolizumab and Epacadostat	Guidance for Restarting Study Treatment	Supportive Care
Grade 1	No action.	Not applicable.	All subjects who experience diarrhea 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. An antidiarrheal can be started.
Grade 2	Withhold pembrolizumab and epacadostat.	May return to treatment if improves to Grade 1. If AE resolves within 4 weeks, subject may restart at the same dose and schedule for both pembrolizumab and epacadostat. For an AE that does not resolve within 4 weeks, epacadostat should be reduced 1 dose level, but pembrolizumab may be restarted at the same dose and schedule. If AE does not resolve within 6 weeks, study treatment with both study drugs should be discontinued or discussed with medical monitor.	An antidiarrheal should be started. If symptoms are persistent for > 1 week, systemic corticosteroids should be initiated (eg, 0.5-1 mg/kg per day of prednisone or equivalent). When symptoms improve to ≤ Grade 1, corticosteroid taper should be started and continued over at least 1 month.
Grades 3 and 4	Discontinue pembrolizumab and epacadostat.	Not applicable. Any exceptions require medical monitor approval.	Treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg per day of prednisone or equivalent. Systemic corticosteroids are indicated. The use of infliximab may be indicated as appropriate. When symptoms improve to ≤ Grade 1, corticosteroid taper should be started and continued over at least 1 month.

5.6.1.4 Procedures and Guidance for Hepatitis

Liver chemistry tests (hepatic transaminase and bilirubin levels) should be monitored and signs and symptoms of hepatotoxicity should be assessed before each dose of pembrolizumab and epacadostat. In subjects with hepatotoxicity, infectious or malignant causes should be ruled out,

and frequency of LFT monitoring should be increased until resolution. Recommendations for managing hepatitis are shown in Table 12.

Table 12: **Recommended Approach for Handling Hepatitis**

Study Drug(s) Associated Hepatitis	Withhold/Discontinue Pembrolizumab and Epacadostat	Guidance for Restarting Study Treatment	Supportive Care
Grade 1	No action.	Not applicable.	Increase frequency of LFT monitoring to twice per week until LFTs return to baseline.
Grade 2	Withhold pembrolizumab and epacadostat.	If AE resolves to ≤ Grade 1 or baseline within 4 weeks, subject may restart at the same dose and schedule for both pembrolizumab and epacadostat. For an AE that does not resolve within 4 weeks, epacadostat should be reduced 1 dose level but pembrolizumab may be restarted at the same dose and schedule. If AE does not resolve within 6 weeks, study treatment with both study drugs should be discontinued.	Increase frequency of LFT monitoring to twice per week until LFTs return to baseline. If elevation persists for > 1 week, systemic corticosteroids should be initiated (eg, 0.5 mg/kg per day of prednisone or equivalent). When symptoms improve to ≤ Grade 1, corticosteroid taper should be started and continued over at least 1 month.
Grades 3 and 4	Discontinue pembrolizumab and epacadostat.	Not applicable. Any exceptions require medical monitor approval.	Increase frequency of LFT monitoring to every 1-2 days. Treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg per day of prednisone or equivalent. When symptoms improve to ≤ Grade 1, corticosteroid taper should be started and continued over at least 1 month.

5.6.1.5 Procedures for Immune-Mediated Dermatitis

Monitor subjects for signs and symptoms of dermatitis such as rash and pruritus. Unless an alternate etiology has been identified, signs or symptoms of dermatitis should be considered immune-mediated. Recommendations for management of dermatitis are shown in Table 13

Table 13: **Recommended Approach for Handling Dermatitis**

irAE	Withhold/Discontinue Pembrolizumab and Epacadostat	Guidance for Restarting Study Treatment	Supportive Care
Grade 1	No action.	Not applicable.	For mild to moderate dermatitis, such as localized rash and pruritus, treat symptomatically. Administer topical or systemic corticosteroids if there is no improvement of symptoms within 1 week.
Grade 2	No action.	Not applicable.	For mild to moderate dermatitis, such as localized rash and pruritus, treat symptomatically. Administer topical or systemic corticosteroids if there is no improvement of symptoms within 1 week.
Grades 3 and 4	Withhold epacadostat and pembrolizumab in subjects with moderate to severe signs and symptoms of rash. Permanently discontinue epacadostat and pembrolizumab in subjects with Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration or by necrotic, bullous, or hemorrhagic manifestations.	If AE resolves to baseline within 4 weeks, subject may restart at the same dose and schedule for both pembrolizumab and epacadostat. For an AE that does not resolve within 4 weeks, epacadostat should be reduced 1 dose level, but pembrolizumab may be restarted at the same dose and schedule. If AE does not resolve within 6 weeks, study treatment with both study drugs should be discontinued or discussed with medical monitor.	Administer systemic corticosteroids at a dose of 1 to 2 mg/kg per day of prednisone or equivalent. When dermatitis is controlled, corticosteroid tapering should occur over a period of at least 1 month.

5.6.1.6 Procedures for Immune-Mediated Neuropathies

Subjects should be monitored for symptoms of motor or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, or paresthesia. Recommendations for management of neuropathies are shown in Table 14.

Table 14: **Recommended Approach for Handling Neuropathies**

irAE	Withhold/Discontinue Pembrolizumab and Epacadostat	Guidance for Restarting Study Treatment	Supportive Care
Grade 1	No action.	Not applicable.	Provide symptomatic treatment.
Grade 2	May withhold pembrolizumab and epacadostat.	If AE resolves to ≤ Grade 1 or baseline within 4 weeks, subject may restart at the same dose and schedule for both pembrolizumab and epacadostat. For an AE that does not resolve within 4 weeks, epacadostat should be reduced 1 dose level but pembrolizumab may be restarted at the same dose and schedule. If AE does not resolve within 6 weeks, study treatment with both study drugs should be discontinued or discussed with medical monitor.	Consider systemic corticosteroids in addition to appropriate symptomatic treatment.
Grades 3 and 4	Discontinue pembrolizumab and epacadostat.	Not applicable. Any exceptions require medical monitor approval.	Consider initiation of systemic corticosteroids at a dose of 1 to 2 mg/kg per day prednisone or equivalent for severe neuropathies. Institute medical intervention as appropriate for management of severe neuropathy.

5.6.1.7 Procedures for Immune-Mediated Endocrinopathies

Subjects should be monitored for clinical signs and symptoms of hypophysitis, adrenal insufficiency (including adrenal crisis), and hyper- or hypothyroidism. Subjects may have fatigue, headache, mental status changes, abdominal pain, unusual bowel habits, and hypotension or have nonspecific symptoms that may resemble other causes such as brain metastasis or underlying disease. Unless an alternate etiology has been identified, signs or symptoms of endocrinopathies should be considered immune-mediated.

Thyroid function tests and clinical chemistries should be monitored at the start of treatment, before each dose and as clinically indicated based on symptoms. In a limited number of subjects, hypophysitis was diagnosed by imaging studies through enlargement of the pituitary gland. Recommendations for management of endocrinopathies are shown in Table 15.

Table 15: **Recommended Approach for Handling Endocrinopathies**

irAE	Withhold/Discontinue Pembrolizumab and Epacadostat	Guidance for Restarting Study Treatment	Supportive Care
Grade 1	No action.	Not applicable.	Provide symptomatic treatment.
Grade 2	May withhold pembrolizumab and epacadostat.	If AE resolves within 4 weeks, subject may restart at the same dose and schedule for both pembrolizumab and epacadostat. For an AE that does not resolve within 4 weeks, epacadostat should be reduced 1 dose level, but pembrolizumab may be restarted at the same dose and schedule. If AE does not resolve within 6 weeks, study treatment with both study drugs should be discontinued.	Initiate systemic corticosteroids treatment at a dose of 1 to 2 mg/kg per day of prednisone or equivalent, and initiate appropriate hormone replacement therapy.
Grade 3	Withhold or discontinue both pembrolizumab and epacadostat.	If AE resolves or is controlled within 4 weeks, subject may restart at the same dose and schedule for both pembrolizumab and epacadostat. For an AE that does not resolve within 4 weeks, epacadostat should be reduced 1 dose level, but pembrolizumab may be restarted at the same dose and schedule. If AE does not resolve within 6 weeks, study treatment with both study drugs should be discontinued or discussed with medical monitor	Consider initiating systemic corticosteroids treatment at a dose of 1 to 2 mg/kg per day of prednisone or equivalent, and initiate appropriate hormone replacement therapy.
Grade 4	Discontinue both pembrolizumab and epacadostat.	Not applicable. Any exceptions require medical monitor approval.	Consider initiation of systemic corticosteroids at a dose of 1 to 2 mg/kg per day of prednisone or equivalent, and initiate appropriate hormone replacement therapy.

5.6.1.8 Procedures for Other Immune-Mediated Adverse Reactions, Including Ocular Manifestations

Epacadostat and pembrolizumab should be permanently discontinued for severe immune-mediated adverse reactions. Systemic corticosteroids treatment should be initiated at a dose of 1 to 2 mg/kg per day of prednisone or equivalent for severe immune-mediated adverse reactions.

Corticosteroid eye drops should be administered to subjects who develop uveitis, iritis, or episcleritis. Epacadostat and pembrolizumab should be permanently discontinued for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy.

5.7 Treatment After Initial Evidence of Radiographic Disease Progression

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

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

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

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

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

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiographic 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 at ≥ 4 weeks confirms PD	No additional imaging required	Discontinue treatment	No additional imaging required	N/A
Repeat scan at ≥ 4 weeks 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 Procedures for Subjects Exhibiting Serotonin Syndrome (SS)

There is a possibility that epacadostat could cause an increase in serotonin levels in the brain that might trigger Serotonin Syndrome (SS), when administered in combination with other serotonergic agents. This syndrome has been most closely associated with use of MAOIs, Demerol®, linezolid, or methylene blue; all of these agents are prohibited during the study.

Serotonin reuptake inhibitors (SSRIs) and serotonin/norepinephrine reuptake inhibitors (SNRIs) are permitted in the study. The following procedures will be implemented if subjects exhibit the signs/symptoms of SS described in Table 17, including tremor; hyperreflexia; spontaneous, ocular, or inducible clonus; together with agitation, fever, diaphoresis, or muscle rigidity:

- Immediately interrupt epacadostat administration.
- Immediately interrupt any SSRI or SNRI administration.
- Provide appropriate medical management of the subject until all signs/symptoms are resolved (eg, IV fluids and/or sympathomimetic amines for hypotension, benzodiazepines for agitation, administration of 5-hydroxytryptamine antagonists such as cyproheptadine).
- If the subject chooses to remain in the study, restart treatment with epacadostat after the SSRI or SNRI has been discontinued no sooner than 5 half-lives have elapsed for the specific SSRI or SNRI in question and after resolution of signs/symptoms of SS. The SSRI or SNRI dosing MAY NOT be restarted.

If the subject chooses to discontinue the study or must restart treatment with SSRI or SNRI, the subject should be scheduled for a follow-up visit. Selective serotonin reuptake inhibitor or SNRI treatment may be initiated 2 weeks after resolution of signs and symptoms of SS.

Table 17. Sign and Symptoms of Serotonin Syndrome

Tremor and hyperreflexia
Spontaneous clonus
Muscle rigidity, temperature > 38°C (100.4°F), and either ocular clonus or inducible clonus
Ocular clonus and either agitation or diaphoresis
Inducible clonus and either agitation or diaphoresis

Study INCB 24360-101 was a Phase 1, multicenter, open-label, dose-escalation study in subjects with refractory solid tumors that used a 3 + 3 design to determine the safety and tolerability, PK, and pharmacodynamics of escalating oral doses of epacadostat. Subjects were administered doses of epacadostat ranging from 50 mg QD to 700 mg BID. Of the 52 subjects treated, 8 subjects (15.4%) had an AE leading to death. Of these 8 subjects, the cause of death was disease progression in 7 subjects and hypoxia in the remaining subject. During the study 25 subjects (48.1%) had a serious adverse event (SAE). The most frequently reported SAEs were disease progression (4 subjects, 7.7%), abdominal pain, nausea, and hypoxia (3 subjects each, 5.8%). Treatment-emergent AEs (TEAEs) were reported in all subjects. Fatigue was the most frequently reported TEAE (36 subjects, 69.2%). Two dose-limiting toxicities (DLTs) occurred; 1 DLT of radiation pneumonitis at the 300 mg BID dose level and 1 DLT of fatigue at the 400 mg BID dose level. A maximum tolerated dose (MTD) was not determined.

An uncommon risk of IDO1 inhibition is an increase in serotonin levels that could precipitate a cluster of AEs termed serotonin syndrome (SS) when administered alone or in combination with other serotonergic agents. This rare syndrome has been associated with some monoamine oxidase inhibitors (MAOIs) and combinations of serotonergic drugs (Boyer and Shannon 2005). 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. In another preclinical study in rats, the effect of epacadostat on the brain extracellular fluid concentration of serotonin was evaluated either alone or when co-administrated with the MOA inhibitor linezolid with or without the SSRI fluoxetine. Both control conditions resulted in 2-6-fold increases in serotonin. In contrast, neither epacadostat alone or in combination with linezolid had an effect on the brain extracellular serotonin levels. These preclinical data suggest that SS is unlikely following treatment with either epacadostat alone or with combination with MAO inhibitors such as linezolid (Zhang, Li, Diamond et al 2016). Therefore, taken together, 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 affect brain serotonin levels.

As of 27 February 2017, 2 subjects across the epacadostat program (958 subjects treated) have reported serotonin syndrome or symptoms of serotonin syndrome and both were mild in their severity and resolved. One subject from study INCB 24360-202 reported chills, increased blood pressure, and temperature (CTC Grade 1) on Cycle 1 day 1 and resolved within one week while dosing was stopped. The subject was taking an SSRI and while he experienced mild symptoms the full constellation of SS was not observed nor could it be ruled out. The SSRI was discontinued and subject was able to restart epacadostat about one week later at the same dose level of 100 mg BID without further incidents. The other subject from study INCB 24360-203 reported CTC Grade 1 tremors and CTC Grade 2 agitation on Cycle 4 day 5 and assessed for SS on Cycle 5 day 1. The subject was not on an SSRI but on a medication for anxiety (alprazolam). The events resolved and the dosing with epacadostat was interrupted for one week. Retreatment started with a lower dose of epacadostat of 50 mg BID PO from 75 mg BID on Cycle 5 day 3. Although this incidence is uncommon, use of MAOIs will be prohibited during the study, and all subjects should be assessed for SS symptoms at an appropriate timeframe after dosing. 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 is observed.

5.9 Diet/Activity/Other Considerations

5.9.1 Diet

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

5.9.2 Contraception

Pembrolizumab and Epacadostat may have adverse effects on a fetus in utero. Furthermore, it is not known if they have 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 defined in section 7.2.2-Reporting of Pregnancy and

Lactation to the Sponsor, to Merck and Incyte. 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.

5.9.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment, 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 and Incyte without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and to Merck and Incyte and followed as described above and in Section 7.2.2.

Pregnancy, in and of itself, is not regarded as an AE unless there is suspicion that study drug may have interfered with the effectiveness of a contraceptive medication or method. When a pregnancy has been confirmed in a subject during maternal or paternal exposure to study drug, the following procedures should be followed in order to ensure subject safety:

- The study drug must be discontinued immediately (female subjects only).
- The investigator must complete and submit the Incyte Clinical Trial Pregnancy form to the sponsor or its designee within **24 hours** of learning of the pregnancy.

Data on fetal outcome and breastfeeding are collected for regulatory reporting and drug safety evaluation. Follow-up should be conducted for each pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications, by following until the first well-baby visit. Pregnancy should be recorded on a Clinical Trial Pregnancy form and reported by the investigator to the sponsor or its designee. Pregnancy follow-up information should be recorded on the same form and should include an assessment of the possible causal relationship to the sponsor's study drug to any pregnancy outcome, as well as follow-up to the first well-baby visit or the duration specified in local regulations, whichever is later. Refer to the Incyte Reference Guide for Completing the Clinical Trial Pregnancy Form.

Any SAE occurring during pregnancy must be recorded on the SAE report form and submitted to the sponsor or designee.

5.9.4 Use in Nursing Women

It is unknown whether Pembrolizumab and Epacadostat are 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.

5.10 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 treating investigator or the PI 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.
- The subject becomes pregnant
- Confirmed radiographic disease progression

  Note: For unconfirmed radiographic disease progression, please see Section 5.7

  Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved,
- Unacceptable adverse experiences
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 24 months of treatment
- *Note: 24 months of study medication is calculated from the date of first dose. Subjects who stop* Pembrolizumab *after 24 months (35 cycles) may be eligible for up to one year of additional study treatment if they progress after stopping study treatment.*
- 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, or the end of the study, whichever occurs first.

5.11 Subject Replacement Strategy

Patients who receive at least one treatment will not be replaced.

5.12 Clinical Criteria for Early Trial Termination

Early trial termination 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 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:	**Treatment Cycles**					**End of Treatment**	**Post-Treatment**		
Treatment Cycle/Title:	Main Study Screening (Visit 1)	1	2	3	4 etc.	Discon	Safety Follow-up	Follow Up Visits[a]	Survival Follow-Up[b]
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	At time of Discon	30 days post discon	Every 12 weeks post discon	Every 12 weeks
Informed Consent	x								
Inclusion/Exclusion Criteria	x								
Demographics and Medical History	x								
Prior and Concomitant Medication Review	x		x	x	x	x	x		
Trial Treatment Administration		x	x	x	x				
Post-study anticancer therapy status								x	x
Survival Status						x			x
Review Adverse Events			x	x	x	x	x		
Full Physical Examination	x	x	x	x	x	x	x		
Directed Physical Examination								x	x
Vital Signs and Weight		x	x	x	x	x	x	x	x
ECOG Performance Status	x	x	x	x	x	x	x	x	x
12-lead ECG	x#	x##	x###		x	x			
Pregnancy Test – Urine or Serum β-HCG*	x								
PT/INR and aPTT**	x								
CBC with Differential**	x		x	x	x	x	x		
Comprehensive Serum Chemistry Panel**	x		x	x	x	x	x		
Hepatitis panel***									
Urinalysis**	x		x	x	x	x	x		
Endocrine Panel**	x		x	x	x	x	x		

Trial Period:	**Treatment Cycles**					**End of Treatment**	**Post-Treatment**		
Treatment Cycle/Title:	Main Study Screening (Visit 1)	1	2	3	4 etc.	Discon	Safety Follow-up	Follow Up Visits[a]	Survival Follow-Up[b]
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	At time of Discon	30 days post discon	Every 12 weeks post discon	Every 12 weeks
Tumor Imaging****	x		x			x		x	
Archival or Newly Obtained Tissue Collection	x								
Correlative Studies Blood Collection (Kynurenine/Trypotophan)	x	x[c]	x[c]			x			

*pregnancy test to be done within 72 hours of starting treatment

**the rest of the blood tests are to be done within 10 days

***for hepatitis panel see table 16 for details

****FDG-PET to be performed if indicated in order to clarify sites of activity, before starting treatment and potentially to assess response. CT scans are performed at the end of the cycle indicated in the chart.

a. follow-up visits until progression for up to 1 year in patients not progressing. b. for one year after last treatment. c. on day 15 of cycle 1 and cycle 2

Triplicate ECG at baseline.

Timed triplicate ECGs (separated by 5 min ± 2 min) at predose and at 2 and 4 hours (± 15 min) postdose.

ECG will be performed on D1 of every other cycle after C2 (eg, C4, C6, C8).

^ ECGs only need to be performed in triplicate if there has been a QT prolongation on study or the ECG shows a clinically significant abnormality not present at baseline.

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

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

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

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 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 Screening Number

Patients who will be screened will receive a Screening Number

7.1.1.7 Assignment of Randomization Number

There will be no randomization in this study.

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

Trial compliance will be assessed regularly before every cycle while on treatment.

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 (see Section 12.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

All AEs of unknown etiology associated with Pembrolizumab or Epacadostat exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (irAE). See Section 5.6.1.1 and the separate guidance document in the administrative binder regarding the identification, evaluation and management of AEs of a potential immunological etiology.

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

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 Directed Physical Exam

For cycles that do not require a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

7.1.2.4 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.

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Appendix 12.3) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart. After Cycle 8 assessment of ECOG status will be performed every other cycle in conjunction with the directed or full physical exam.

7.1.2.6 Tumor Imaging and Assessment of Disease

Adequate imaging to assess the disease stage and burden will be performed before starting treatment. An FDG-PET/CT scan with diagnostic CT scan is recommended as part of the staging procedures at screening. If the FDG-PET was positive, it will be repeated when indicated.

7.1.2.7 Tumor Tissue Collection and Correlative Studies Blood Sampling

Archival tumor material will be obtained for histological confirmation and will be used for immunohistochemistry for PDL-1 expression and for Next-Generation sequencing. Submssion of a tumor block or 20 unstained slides is acceptable. Whenever feasible a new biopsy will be obtained before starting treatment, and normal blood will be collected for Next-Generation Sequencing.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below.

Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 18.

Table 18: Local Laboratory Tests: Required Analytes

Serum Chemistries	Hematology	Urinalysis With Microscopic Examination	Hepatitis Screening	Coagulation
Albumin Alkaline phosphatase ALT AST Bicarbonate Blood urea nitrogen Calcium Chloride Creatinine Glucose Lactate dehydrogenase Phosphate Potassium Sodium Total bilirubin Direct bilirubin (if total bilirubin is elevated above ULN) Total protein Uric acid Troponin Creatine Kinase (the MB fraction if total is elevated)	Complete blood count, including: Hemoglobin Hematocrit Platelet count Red blood cell count White blood cell count Differential count, including: Basophils Eosinophils Lymphocytes Monocytes Neutrophils Absolute values must be provided for: WBC differential laboratory results: Lymphocytes Neutrophils	Color and appearance pH and specific gravity Bilirubin Glucose Ketones Leukocytes Nitrite Occult blood Protein Urobilinogen	Hepatitis B surface antigen Hepatitis B core antibody HBV-DNA HCV antibody HCV-RNA	PT PTT INR
		Endocrine Monitoring	**Tumor Markers**	**Pregnancy Testing**
		ACTH Serum cortisol Prolactin TSH Free thyroxine (T4) Total triiodothyronine (T3) Serum testosterone	If elevated	Female subjects of childbearing potential only require a serum test at screening (must be performed within 72 hours before the first dose of study drug) and at safety follow-up. Pregnancy tests (serum or urine) should be repeated if required by local regulations.

ACTH = adrenocorticotropic hormone.
Note: Additional tests may be required, as agreed by investigator and sponsor, based on emerging safety data.

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.

7.1.3.1 Pharmacokinetic/Pharmacodynamic Evaluations

There will be no blood or urine taken for pharmacokinetic analysis.

Levels of tryptophan and kynurenine will be evaluated by liquid chromatography with tandem mass spectrometry to monitor systemic activity in modulating the IDO1 enzyme. PI will request its measurement to Incyte Corporation (Wilmington, DE) or Incyte's designee. A total of 5mL of blood will be drawn. Blood samples will be collected for pharmacodynamics studies (Plasma Tryptophan/ Kynurenine Ratio) from all participating subjects at Baseline, C1D15, and C2D1 for PD analysis for epacadostat. Patients should be fasting prior to blood collection as food intake can affect Tryptophan levels and unfasted samples can make Tryptophan/Kynurenine ratios difficult to interpret. The procedures for specimen collection, handling and shipping are as follows:

a. A total of 5mL blood will be collected into a sodium heparinized tube.
After obtaining sample, immediately invert collection tube several times gently to mix.
b. Within 1 hour of collection, centrifuge at 400 x g for 10 minutes to separate cells and plasma.
c. Transfer plasma equally into (1) 2 mL (Aliquot A) and (1) 2 mL (Aliquot B) cryovials with appropriate labeling using standard laboratory technique.
d. Freeze on dry ice or at - 20ºC to - 80ºC immediately.
e. Store aliquots in a freezer set to maintain a temperature of - 70°C or colder until ready for shipment. Samples must be maintained in the frozen state until assayed.
f. Ship frozen Plasma Aliquot A samples daily with a 2-day supply of dry ice to the designated lab for priority (next morning) overnight delivery using the insulated container and pre-printed air bill provided by study. If you are unable to ship the sample the same day, the next business day is acceptable.
g. Aliquot B samples will be shipped monthly with a 2-day supply of dry ice to the designated lab (A samples and B samples from the same individual at the same time point should not be shipped together).
h. Include a copy of the requisition with each shipment.

7.1.3.1.1 Blood Collection for Serum Pembrolizumab or Epacadostat

There will be no blood collection for pharmacokinetic analysis.

7.1.3.1.2 Blood Collection for Anti-Pembrolizumab Antibodies

There will be no sample collection for antibodies against Pembrolizumab.

7.1.4 Other Procedures

7.1.4.1 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 and Epacadostat may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 7.1.5.2.1. 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).

7.1.4.2 Blinding/Unblinding

This is an open label study.

7.1.5 Visit Requirements

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

7.1.5.1 Screening

Once the subject has been identified, he/she will be subjected to screening procedures as identified in section 6.0.

7.1.5.1.1 Screening Period

Within 28 days from start of treatment.

7.1.5.2 Treatment Period

Patients will be treated within a week from registration, every 3 weeks (one cycle) and will continue treatment until there are signs of benefit, but not beyond progression unless they are deemed to be clinically stable or clinically improved (see 5.8). The maximum treatment duration is 24 months.

7.1.5.2.1 Retreatment-Second Course Phase

Subjects who have stable disease (SD), PR, or CR after receiving 35 pembrolizumab treatments may be eligible for up to an additional 17 cycles (approximately 1 year) of pembrolizumab treatment. This retreatment is termed the Second Course Phase of this trial and will only be available if the trial remains open and the subject meets the following conditions:

- Had SD, PR, or CR and stopped treatment after completion of 35 administrations (approximately 2 years) of pembrolizumab either in the Initial Treatment Phase or in a combination of the Initial Treatment and the Continued Treatment Phase OR stopped trial treatment for reasons other than disease progression or intolerability ***AND***

- Experienced an investigator-determined radiographic disease progression by RECIST 1.1 after stopping initial treatment, and

- No new anticancer treatment was administered after the last dose of trial treatment, and

- The subject meets all of the safety parameters listed in the inclusion criteria and none of the safety parameters listed in the exclusion criteria, and

- The trial is ongoing.

7.1.5.3 Post-Treatment Visits

7.1.5.3.1 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.

7.1.5.4 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 12weeks (84 ± 7 days) by radiologic imaging to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study or if the subject begins retreatment with Pembrolizumab. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

Subjects who are eligible to receive retreatment with Pembrolizumab will move from the follow-up phase to the Second Course Phase (Section 7.1.5.2.1) when they experience disease progression.

7.1.5.4.1 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 every 12

weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

7.2 Assessing and Recording Adverse Events

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

Adverse events may occur during the course of the use of Merck/Incyte products 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.

Adverse events may also occur in screened subjects during any pre-allocation baseline period as a result of a protocol-specified intervention, including washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

All adverse events will be recorded from the time the consent form is signed through 30 days following cessation of treatment 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.

Adverse events will not be collected for subjects during the pre-screening period (for determination of archival tissue status) as long as that subject has not undergone any protocol-specified procedure or intervention. If the subject requires a blood draw, fresh tumor biopsy etc., the subject is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting.

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

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for Pembrolizumab and/or Epacadostat by 20% over the prescribed dose. No specific information is available on the treatment of overdose of Pembrolizumab or Epacadostat. In the event of

overdose, drugs should be discontinued and 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 the overdose occurs 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 (Attn: Multi-Site Coordinator FAX 202-687-3821) and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220) and Incyte (see below)

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor and to Merck

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 hydatiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor (Attn: CRMO Office FAX 202-687-3821; and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220) and Incyte (see below).

7.2.3 Immediate Reporting of Adverse Events to the Sponsor and to Merck

7.2.3.1 Serious Adverse Events

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

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is 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 19 for additional details regarding each of the above criteria.

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

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 the consent is signed through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to Merck or Incyte product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety and Incyte (see below).

Non-serious Events of Clinical Interest will be forwarded to Merck Global Safety and Incyte (see below) 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 or Incyte product 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 and Incyte.

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-993-1220 and Incyte as per their reporting guidelines below.

All Serious Adverse Events ("SAE") 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 provide any additional reports agreed upon by the Institution or Principal Investigator and Incyte's contact below. SAE Reports will be sent to the email address provided below. By sending to this e-mail address, the Incyte Pharmacovigilance group and the Incyte clinical operations project manager will receive copies of the reports. This process will be tested and established before the first patient is enrolled in the trial. Notwithstanding anything to the contrary herein, Institution or Principal Investigator will have the primary responsibility of reporting adverse events ("AE") to regulatory authorities.

Copies of IND safety reports submitted to the FDA by the Institution will be shared with the contact below so that these reports can be evaluated and included in investigator brochure or Incyte IND safety submissions as required to ensure safety of other patients who are receiving the product from Incyte for sponsored trials.

Incyte Corporation: IncytePhVOpsIST@incyte.com for e-mail transmission of individual SAE reports;

Safety Contacts: Kathy Lenard Roberts, Exec. Dir, Incyte Pharmacovigilance, Phone: 302-498-6727, Email: kroberts@incyte.com

Incyte reporting requirements for pregnancy:

Data on fetal outcome are collected for regulatory reporting and drug safety evaluation. Follow-up should be conducted for each pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Within 30 days of learning of the pregnancy, the investigational site completes the Clinical Trial Pregnancy Form (sections I, II, and question 18 in section III) or equivalent, and e-mails the report to Incyte at ***IncytePhVOpsIST@incyte.com***.

Within 30 days of learning of the outcome of the pregnancy (delivery, termination, or miscarriage), the investigational site completes the Clinical Trial Pregnancy Form (sections II, III, IV, and V) or equivalent, and e-mails the report to Incyte at ***IncytePhVOpsIST@incyte.com***.

NOTE: If a woman has a positive pregnancy test at Baseline, the investigational site completes Clinical Trial Pregnancy Form (sections I, II, and III (question 18)) or equivalent and e-mails the report to Incyte at ***IncytePhVOpsIST@incyte.com***, as per established timelines.

Any SAE occurring during pregnancy must be reported to Incyte as an SAE, in accordance with Section 3 of the Serious Adverse Event Reporting Plan, as provided by Incyte.

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

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

7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220) and Incyte (see section above)

Events of clinical interest for this trial include:

1. an overdose of Pembrolizumab and/or Epacadostat product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of

normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

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

ECIs that occur in any subject from the date of first dose through 90 days following cessation of treatment, or the initiation of a new anticancer therapy, whichever is earlier, whether or not related to the Merck's product, must be reported within 24 hours to the Sponsor and to Merck Global Safety and Incyte (see section above) within 2 working days.

7.2.4 Evaluating Adverse Events

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

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

Table 19. 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 Pembrolizumab and/or Epacadostat 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 Pembrolizumab and/or Epacadostat to be discontinued?	
Relationship to test drug	Did Pembrolizumab and/or Epacadostat cause the adverse event? The determination of the likelihood that Pembrolizumab and/or Epacadostat 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 product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely Pembrolizumab and/or Epacadostat caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to Pembrolizumab and/or Epacadostat 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 Pembrolizumab and/or Epacadostat? 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 Merck product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Were Pembrolizumab and/or Epacadostat 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 Pembrolizumab and Epacadostat; or (3) the trial is a single-dose drug trial); or (4) Pembrolizumab and Epacadostat were only used one time.)
	Rechallenge	Was the subject re-exposed to Pembrolizumab and Epacadostat 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 product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY Pembrolizumab and/or Epacadostat, OR IF REEXPOSURE TO THE MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding Pembrolizumab and/or Epacadostat 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 product relationship).**	
Yes, there is a reasonable possibility of Merck product relationship.	There is evidence of exposure to Pembrolizumab and/or Epacadostat. The temporal sequence of the AE onset relative to the administration of drugs is reasonable. The AE is more likely explained by drug exposure than by another cause.	
No, there is not a reasonable possibility Merck product relationship	Subject did not receive Pembrolizumab and/or Epacadostat OR temporal sequence of the AE onset relative to administration of drugs is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)	

7.2.5 Sponsor Responsibility for Reporting Adverse Events

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

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

This is a phase II study of MK-3475 in thymic carcinoma patients who recurred after at least one prior chemotherapy regimen. The primary endpoint is response rate; secondary endpoints are Progression-Free Survival, Overall Survival and treatment tolerability. Responses will be assessed according to RECIST 1.1; progression-free survival is defined as time between start of treatment and tumor progression or death, whichever comes first; survival is the time between start of treatment and death or last follow-up. Furthermore exploratory studies will be performed on archival tumor material (PDL-1 expression, next-generation sequencing), and fresh biopsies (culturing; next-generation sequencing).

8.2 Statistical Analysis Plan

Simon's two-stage optimal design is used. The null hypothesis that the true response rate is 5% will be tested against a one-sided alternative. In the first stage, 21 patients will be accrued. If there are 1 or fewer responses in these 21 patients, the study will be stopped. Otherwise, 20 additional patients will be accrued for a total of 41. The null hypothesis will be rejected if 5 or more responses are observed in 41 patients. This design yields a type I error rate of 5% and power of 90% when the true response rate is 20%. Should a need for unplanned interim analysis arise, the significance of the response test will be evaluated based on the reverse curtailing SCRPT method (see, Tan M, Xiong X. A Flexible Multi-Stage Design for Phase II Oncology Trials. Pharmaceutical Statistics. 2011;10:369-73). Should the first stage indicate futility, the SCPRT method will also be used to assess the chance for a trend reversal at the end second stage. Kaplan–Meier estimator will be used for progression free survival and overall survival analysis. The response rate, tolerability rate and PDL-1 expression incidence rate will be separately estimated as a binomial proportion with 95% exact Clopper-Pearson confidence interval using exact binomial calculation.

The results of NextGen sequencing will be analyzed assessing the relation between response and presence of any mutation, and response (percentage of tumor change) and number of mutation per sample by regression analysis with proper control of false discovery rate, using the regularized statistical learning model with cross validation.

The results of the conditionally reprogrammed cell cultures will be analyzed in a descriptive manner. We will define whether the tumors are heterogeneous (i.e. have different morphologies and/or somatic mutation spectra) and whether these are related to response, again with regularized statistical model.

AMENDED STATISTICAL CONSIDERATIONS FOR THE COMBINATION OF PEMBROLIZUMAB AND EPACADOSTAT

8.3 Statistical Analysis Plan Summary

The amended phase II study of Pembrolizumab and Epacadostat is for thymic carcinoma patients who recurred after at least one prior chemotherapy regimen. The primary endpoint is response rate; secondary endpoints are Progression-Free Survival, Overall Survival and treatment tolerability. Responses will be assessed according to RECIST 1.1; progression-free survival is defined as time between start of treatment and tumor progression or death; survival is the time between start of treatment and death. Furthermore exploratory studies will be performed on archival tumor material (PDL-1 expression, next-generation sequencing), and fresh biopsies (culturing; next-generation sequencing).

8.4 Statistical Analysis Plan

In the amended protocol a new cohort of patients with advanced thymic carcinoma will be treated with the combination of pembrolizumab and epacadostat. The response rate that is expected is 45%, comparing to a constant of 25%, which is roughly the response rate with pembrolizumab and sunitinib as single agents, the sample size is **26**, with a type I error rate of 10%, power 80%, and one sided test.

Kaplan–Meier estimator will be used for progression free survival and overall survival analysis. The response rate, tolerability rate and PDL-1 expression incidence rate will be separately estimated as a binomial proportion with 95% exact Clopper-Pearson confidence interval using exact binomial calculation.

The results of NextGen sequencing will be analyzed assessing the relation between response and presence of any mutation, and response (percentage of tumor change) and number of mutation per sample by regression analysis with proper control of false discovery rate, using the regularized statistical learning model with cross validation.

The results of the conditionally reprogrammed cell cultures will be analyzed in a descriptive manner. We will define whether the tumors are heterogeneous (i.e. have different morphologies and/or somatic mutation spectra) and whether these are related to response, again with regularized statistical model.

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 as summarized in Table 20.

Table 20. Product Descriptions

Product Name & Potency	Dosage Form
MK-3475 100 mg/ 4mL	Solution for Injection
Epacadostat 100 mg BID	25 and 100 mg Tablets

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 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 Confidentiality

10.1.1 Confidentiality of Data

The investigator affirms that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board,

other expert committees (LCCC Clinical Research Committee and Data Safety Monitoring Committee), Food and Drug Administration; and employees working on this study, only under an appropriate understanding of confidentiality. Data generated by this trial will be considered confidential by the investigators, except to the extent that it is included in publications.

10.1.2 Confidentiality of Subject Records

The investigator agrees that the Sponsor, IRB, or regulatory authority representatives may consult and/or copy trial documents in order to verify case report form data. By signing the consent form, the subject agrees to this process. The subject will be identified by a unique code only on all case report forms and correlative science specimens.

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

10.2 Compliance with Financial Disclosure Requirements

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

10.3 Compliance with Law, Audit and Debarment

The investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with the protocol; generally accepted standards of Good Clinical Practice; and all applicable federal, state, and local laws, rules and regulations relati8ng to the conduct of the clinical trial.

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

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

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

10.5 Data Safety Monitoring Plan

The Georgetown Lombardi Comprehensive Cancer Center will be responsible for the data and safety monitoring of this multi-site trial. As this study is an investigator initiated study Phase II study utilizing a non-FDA approved drug for which the PI holds the IND it is considered a high risk study which requires real-time monitoring by the PI and study team and quarterly reviews by the LCCC Data and Safety Monitoring Committee (DSMC).

The Principal Investigator and the Co-Investigators will review the data including safety monitoring at their weekly institution based disease group meetings and on monthly disease group teleconferences.

All Severe Adverse Events (SAEs) are required to be reported to the IRB. Based on SAEs, the IRB retains the authority to suspend further accrual pending more detailed reporting and/or modifications to further reduce risk and maximize the safety of participating patients.

Progress on the trial and the toxicities experienced will be reviewed by the LCCC Data and Safety Monitoring Committee every 4 months from the time the first patient is enrolled on the study. Results of the DSMC meetings will be forwarded to the IRB with recommendations regarding need for study closure.

DSMC recommendations should be based not only on results for the trial being monitored as well as on data available to the DSMC from other studies. It is the responsibility of the PI to ensure that the DSMC is kept apprised of non-confidential results from related studies that become available. It is the responsibility of the DSMC to determine the extent to which this information is relevant to its decisions related to the specific trial being monitored.

A written copy of the DSMC recommendations will be given to the trial PI and the IRB. If the DSMC recommends a study change for patient safety or efficacy reasons the trial PI must act to implement the change as expeditiously as possible. In the unlikely event that the trial PI does not concur with the DSMC recommendations, then the LCCC Deputy Director must be informed of the reason for the disagreement. The trial PI, DSMC Chair, and the LCCC Deputy Director will be responsible for reaching a mutually acceptable decision about the study and providing details of that decision to the IRB. Confidentiality must be preserved during these discussions. However, in some cases, relevant data may be shared with other selected trial investigators and staff to seek advice to assist in reaching a mutually acceptable decision.

If a recommendation is made to change a trial for reasons other than patient safety or efficacy the DSMC will provide an adequate rationale for its decision. If the DSMC recommends that the trial be closed for any reason, the recommendation will be reviewed by the LCCC Deputy Director. Authority to close a trial for safety reasons lies with the IRB, with the above described input from DSMC and the LCCC Deputy Director.

10.6 Data Management

Patient data will be entered into the on-line accessible Oracle Clinical database. This database is housed at Georgetown, but is accessible anywhere there is internet access. All research coordinators and data managers will attend an on-line training session to learn how to accurately enter any data into the Oracle data base. All screening data should be entered prior to starting therapy, and all ongoing patient data should be entered within one week of each patient visit. The LCCC QA Manager will be reviewing all online data on a regular basis to ensure compliance.

10.7 Multi-Site Study Coordination

The multi-site coordinator in the Georgetown Lombardi Comprehensive Cancer Center CRMO will have responsibility for coordination among participating sites. She will be the main point of contact for the investigators for any study related concerns and to double check eligibility for each patient considered for enrollment. She will be the point of contact for data managers for data entry questions. She will play a major role in regulatory coordination of this study, specifically by:

a) Reviewing and confirming all study-related adverse events

b) Submitting all SAE reports to the Georgetown IRB, FDA, and Merck (The research coordinators at collaborating sites will prepare SAE reports for subjects treated at their individual site, and the multi-site coordinator will submit the final report to all necessary parties).

c) Gathering and preparing all primary source data for review/audit.

Contact: CRMO Office Ph: 202-687-1569 Fax: 202-687-3821

11.0 LIST OF REFERENCES

1. Disis ML. Immune regulation of cancer. J Clin Oncol 2010; 28(29):4531-8.

2. Dudley ME, Wunderlich JR, Yang JC, Sherry RM, Topalian SL, Restifo NP, et al. Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. J Clin Oncol 2005;23(10):2346-57.

3. Hunder NN, Wallen H, Cao J, Hendricks DW, Reilly JZ, Rodmyre R, et al. Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1. N Engl J Med 2008;358(25):2698-703.

4. Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisted. Annu Rev Immunol 2005;23:515-48.

5. Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. PNAS 2001;98(24):13866-71.

6. Zhang X, Schwartz JC, Guo X, Bhatia S, Cao E, Lorenz M, et al. Structural and functional analysis of the costimulatory receptor programmed death-1. Immunity 2004;20:337-47.

7. Chemnitz JM, Parry RV, Nichols KE, June CH, Riley JL. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. J Immunol 2004;173:945-54.

8. Sheppard KA, Fitz LJ, Lee JM, Benander C, George JA, Wooters J et al. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. FEBS Lett 2004;574:37-41.

9. Riley JL. PD-1 signaling in primary T cells. Immunol Rev 2009;229:114-25.

10. Parry RV, Chemnitz JM, Frauwirth KA, Lanfranco AR, Braunstein I, Kobayashi SV, et al. CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. Mol Cell Biol 2005;25:9543-53.

11. Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunol Rev 2010;236:219-42.

12. Agata Y, Kawasaki A, Nishimura H, Ishida Y, Tsubata T, Yagita H, et al. Expression of the PD-1 antigen on the surface of stimulated mouse T and B lymphocytes. Int Immunol 1996;8(5):765-72.

13. Vibhakar R, Juan G, Traganos F, Darzynkiewicz Z, Finger LR. Activation induced expression of human programmed death-1 gene in T-lymphocytes. Exp Cell Res 1997;232:25-8.

14. Nishimura H, Honjo T, Minato N. Facilitation of β selection and modification of positive selection in the thymus of PD-1-deficient mice. J Exp Med 2000;191(5):891-7.

15. Brown JA, Dorfman DM, Ma F-R, Sullivan EL, Munoz O, Wood CR, et al. Blockade of programmed death-1 ligands on dendritic cells enhances T cell activation and cytokine production. J Immunol 2003;170:1257-66.

16. Dong H, Strome SE, Salomao DR, Tamura H, Hirano F, Flies DB, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Nat Med 2002;8(8):793-800.

17. Sharpe AH, Freeman GJ. The B7-CD28 superfamily. Nature 2002;2:116-26.

18. Thompson RH, Dong H, Lohse CM, Leibovich BC, Blute ML, Cheville JC, et al. PD-1 expressed by tumor-infiltrating immune cells and is associated with poor outcome for patients with renal cell carcinoma. Clin Caner Res 2007;13(6):1757-61.

19. Nomi T, Sho M, Akahori T, Hamada K, Kubo A, Kanehiro, H, et al. Clinical significance and therapeutic potential of the programmed death-1 ligand/programmed death-1 pathway in human pancreatic cancer. Clin Cancer Res 2007;13:2151-7.

20. Gao Q, Wang XY, Qiu SJ, Yamato I, Sho M, Nakajima Y, et al. Overexpression of PD-L1 significantly associates with tumor aggressiveness and postoperative recurrence in human hepatocellular carcinoma. Clin Cancer Res 2009;15: 971-9.

21. Hamanishi J, Mandai M, Iwasaki M, Okazaki T, Tanaka Y, Yamaguchi K, et al. Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer. Proc Natl Acad Sci USA 2007;104:3360-5.

22. Fourcade J, Kudela P, Sun Z, Shen H, Lenzner D, Guillaume P, et al. PD-1 is a regulator of NY-ESO-1-specific CD8+ T cell expansion in melanoma patients. J Immunol 2009;182:5240-9.

23. Kelly, R. J., Petrini, I., Rajan, A., Wang, Y., & Giaccone, G. (2011). Thymic malignancies: From clinical management to targeted therapies. Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology, 29(36), 4820-4827.

24. Kelly, R. J., Browne, S. K., Rajan, A., & Giaccone, G. (2010). Thymoma-associated paraneoplastic polymyositis. Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology, 28(22), e378.

25. Rajan, A., Kotlyar, D., & Giaccone, G. (2013). Acute autoimmune hepatitis, myositis, and myasthenic crisis in a patient with thymoma. Journal of Thoracic Oncology : Official Publication of the International Association for the Study of Lung Cancer, 8(10), e87-8.

26. Rajan, A., Carter, C. A., Berman, A., Cao, L., Kelly, R. J., Thomas, A., et al. (2014). Cixutumumab for patients with recurrent or refractory advanced thymic epithelial tumours: A multicentre, open-label, phase 2 trial. The Lancet Oncology, 15(2), 191-200.

27. Burbelo, P. D., Browne, S. K., Sampaio, E. P., Giaccone, G., Zaman, R., Kristosturyan, E., et al. (2010). Anti-cytokine autoantibodies are associated with opportunistic infection in patients with thymic neoplasia. Blood, 116(23), 4848-4858.

28. Lemma, G. L., Lee, J. W., Aisner, S. C., Langer, C. J., Tester, W. J., Johnson, D. H., et al. (2011). Phase II study of carboplatin and paclitaxel in advanced thymoma and thymic carcinoma. Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology, 29(15), 2060-2065.

29. Giaccone, G., Ardizzoni, A., Kirkpatrick, A., Clerico, M., Sahmoud, T., & van Zandwijk, N. (1996). Cisplatin and etoposide combination chemotherapy for locally advanced or metastatic thymoma. A phase II study of the European Organization for Research and Treatment of Cancer lung cancer cooperative group. Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology, 14(3), 814-820.

30. Giaccone, G., Rajan, A., Ruijter, R., Smit, E., van Groeningen, C., & Hogendoorn, P. C. (2009). Imatinib mesylate in patients with WHO B3 thymomas and thymic carcinomas. Journal of Thoracic Oncology : Official Publication of the International Association for the Study of Lung Cancer, 4(10), 1270-1273.

31. Giaccone, G., Rajan, A., Berman, A., Kelly, R. J., Szabo, E., Lopez-Chavez, A., et al. (2011). Phase II study of belinostat in patients with recurrent or refractory advanced thymic epithelial tumors. Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology, 29(15), 2052-2059.

32. Thomas, A., Rajan, A., Berman, A., Brzezniak, C.E., Splitter, A.J., Carter, C.A., Guha, U., Wang, Y., Szabo, E., Loehrer, P.J., Giaccone, G. Phase II trial of sunitinib in patients with thymic epithelial tumors (TET). J Clin Oncol 32:5s, 2014 (suppl; abstr 7525)

33. Wang Y, Meltzer PS, Lau C, Thomas A, Rajan A, Giaccone G. Recurrence of epigenetic gene mutations in thymic epithelial carcinomas revealed by targeted exome sequencing of cancer-associated genes. J Clin Oncol 32:5s, 2014 (suppl; abstr 7529).

34. Liang, S. C., Latchman, Y. E., Buhlmann, J. E., Tomczak, M. F., Horwitz, B. H., Freeman, G. J., et al. (2003). Regulation of PD-1, PD-L1, and PD-L2 expression during normal and autoimmune responses. European Journal of Immunology, 33(10), 2706-2716.

35. Padda, S.K., Riess, J., Schwartz, E.J., Tian, L., Kohrt, H.E., Neal, J.W., Natkunam, Y., West, R.B., Wakelee, H.A. Programmed death receptor ligand-1 (PD-L1) expression in a thymoma (T) tissue microarray (TMA). J Clin Oncol 32:5s, 2014 (suppl; abstr 7606)

36. Hamid O, Robert C, Daud A, Hodi FS, Hwu FS, Hwu WJ, Kefford R, Wolchok JD, Hersey P, et al. Safety and tumor response with lambrolizumab (anti PD-1) in melanoma. NEJM 2013, 369, 134-144.

37. Suprynowicz FA, Upadhyay G, Krawczyk E, Kramer SC, Hebert JD, Liu X, Yuan H, Cheluvaraju C, Clapp PW, Boucher RC Jr, Kamonjoh CM, Randell SH, Schlegel R. Conditionally reprogrammed cells represent a stem-like state of adult epithelial cells. Proc Natl Acad Sci U S A. 2012 Dec 4;109(49):20035-40.

38. Petrini I, Meltzer PS, Kim IK, Lucchi M, Park KS, Fontanini G, Gao J, Zucali PA, Calabrese F, Favaretto A, Rea F, Rodriguez-Canales J, Walker RL, Pineda M, Zhu YJ, Lau C, Killian KJ, Bilke S, Voeller D, Dakshanamurthy S, Wang Y, Giaccone G. A specific missense mutation in GTF2I occurs at high frequency in thymic epithelial tumors. Nat Genet. 2014 Aug;46(8):844-9.

39. Vogelstein B, Papadopoulos N, Velculescu VE, Zhou S, Diaz LA Jr, Kinzler KW. Cancer genome landscapes. Science. 2013 Mar 29;339(6127):1546-58.

40. Boyer EW, Shannon M. The serotonin syndrome. New Eng J Med 2005;352:1112-1120.

41. Y. Zhang, Y. Li, S. Diamond, S. Yeleswaram (AAPS, abstract/poster 2016). Effects of Epacadostat with Co-Administration of Linezolid on Brain Extracellular Fluid Concentrations of Serotonin: An Intracerebral Microdialysis Study in Sprague-Dawley Rats

12.0 APPENDICES

12.1 WHO histological classification (Rosai J SL. *Histological typing of tumours of the thymus*. 2nd edition ed. New York: Springer; 1999)

Type	Description
A	A tumor composed of a population of neoplastic thymic epithelial cells having spindle/oval shape, lacking nuclear atypia, and accompanied by few or no non-neoplastic lymphocytes.
AB	A tumor in which foci having the features of type A thymoma are admixed with foci rich in lymphocytes.
B1	A tumor that resembles the normal functional thymus in that it combines large expanses having an appearance practically indistinguishable from normal thymic cortex with areas resembling thymic medulla.
B2	A tumor in which the neoplastic epithelial component appears as scattered plump cells with vesicular nuclei and distinct nucleoli among a heavy population of lymphocytes. Perivascular spaces are common and sometimes very prominent. A perivascular arrangement of tumor cells resulting in a palisading effect may be seen.
B3	A type of thymoma predominantly composed of epithelial cells having a round or polygonal shape and exhibiting no or mild atypia. They are admixed with a minor component of lymphocytes, resulting in a sheet-like growth of the neoplastic epithelial cells.
C	A thymic tumor exhibiting clear-cut cytologic atypia and a set of cytoarchitectural features no longer specific to the thymus, but rather analogous to those seen in carcinomas of other organs. Type C thymomas lack immature lymphocytes; whatever lymphocytes may be present are mature and usually admixed with plasma cells.

12.2 Masaoka staging system (Masaoka A, Monden Y, Nakahara K, Tanioka T. Follow-up-study of thymomas with special reference to their clinical stages. *Cancer* 1981; 48: 2485-92).

Stage		Description
I		Tumor remains completely encapsulated
II	A	Microscopic transcapsular invasion
	B	Macroscopic invasion into surrounding fatty tissue or grossly adherent to (but not through) mediastinal pleural or pericardium
III		Macroscopic invasion into neighboring organs (i.e. pericardium, great vessels, lung)
	A	Without invasion of great vessels
	B	With invasion of great vessels
IV	A	Pleural or pericardial dissemination
	B	Lymphogenous or hematogenous metastasis

12.3 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).

Grade	Description
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

12.4 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)

12.5 Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumors

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

* 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.