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COLUMBIA UNIVERSITY MEDICAL CENTER

Herbert Irving Comprehensive Cancer Center Protocol

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TITLE: A Phase II Study of Epacadostat and Pembrolizumab in Patients with Imatinib-Refractory Advanced Gastrointestinal Stromal Tumors

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Protocol Signature Page

I confirm that I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable ICH guidelines for good clinical practices, and the applicable federal, state, and local laws, rules, and regulations relating to the conduct of the protocol. I have read and understand the information in the Investigators' Brochure (or Manufacturer's Brochure) regarding the risks and potential benefits. I will promptly submit the protocol to the applicable IRB for review and approval. Once the protocol has been approved by the IRB, I understand that any modification made during the course of the study must first be approved by the IRB, prior to implementation except when such modification is made to remove an immediate hazard to the subject. I certify that I, and the study staff, have received the requisite training to conduct this research protocol. I agree to maintain adequate and accurate records in accordance with Columbia University and Herbert Irving Comprehensive Cancer Center policies, Federal, state and local laws and regulations. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Instructions to Principal Investigator: Sign and Date this signature page and print your name. Return the original, completed and signed to the Clinical Protocol & Data Management Office. Retain a copy in the regulatory binder.

_____ _____
Signature of Principal Investigator Date

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Principal Investigator Name (Print)

_____
NAME OF INSTITUTION

PROTOCOL SYNOPSIS

Title	A Phase II Study of Epacadostat and Pembrolizumab in Patients with Imatinib-Refractory Advanced Gastrointestinal Stromal Tumors
Short Title	IDO and PD-1 inhibition in imatinib-refractory GIST
Phase	Phase II
Methodology	This is a multi-center, single-arm phase II study of combined IDO and PD-1 inhibition with epacadostat and pembrolizumab in imatinib-refractory advanced GIST patients. This study will use a primary endpoint of overall response rate.
Study Duration	24 months
Study Center(s)	Multicenter: 2 sites Columbia University Medical Center University of Michigan
Objectives	**Primary Objective:** a. To assess the efficacy of combined IDO and PD-1 inhibition in a single arm phase II trial of epacadostat and pembrolizumab in patients with advanced imatinib-refractory GIST, using a primary endpoint of overall response rate using RECIST v1.1 criteria. **Secondary Objectives:** a. To evaluate the progression free survival (PFS) of patients with advanced GIST treated with epacadostat and pembrolizumab using RECIST v1.1 criteria. b. To evaluate the overall survival (OS) of patients with advanced GIST treated with epacadostat and pembrolizumab. c. To evaluate response rate using Choi criteria. d. To evaluate the safety and tolerability of combined epacadostat and pembrolizumab treatment in the advanced GIST population. **Exploratory Objectives:** a. To correlate the effect of IDO inhibition with response to therapy by evaluating baseline and on-treatment serum samples for tryptophan metabolite levels. b. To characterize the effect of combined therapy with IDO and PD-1 inhibition on T-cell subsets by evaluating baseline and on-treatment tumor samples for changes in the T-effector to T-regulator cell ratio using immunohistochemistry. c. To characterize the relationship between PD-L1 status and response to combined IDO and PD-1 inhibition.

Number of Subjects	Total maximum accrual of subjects: 23 patients

Diagnosis and Main Inclusion Criteria	**Study Population:**
	Subjects with unresectable or metastatic GIST who have progressed on imatinib.
	
	Key Inclusion Criteria:
	• Age 18 years or older.
	• Histologically confirmed unresectable or metastatic GIST.
	• Clinical or radiographic progression on first-line imatinib. Those who were taken off of imatinib for intolerance must have progressed on at least one other TKI.
	• Subjects must have received ≥1 prior systemic therapy (including imatinib). A maximum of 4 prior therapies for metastatic disease are allowed.
	• ECOG performance status ≤1.
	• Estimated life expectance of ≥ 3 months.
	• Laboratory parameters within the following Protocol-defined range. All screening laboratory tests should be performed within 28 days of treatment initiation and must be independent of hematopoietic growth factor support.
	  • Absolute neutrophil count ≥ 1.5 x 10^9/L.
	  • Platelets ≥ 100 x 10^9/L.
	  • Hemoglobin ≥ 9 g/dL (transfusion is acceptable to meet this criteria).
	  • Serum creatinine ≤ 1.5 x institutional upper limit of normal (ULN) OR calculated creatinine clearance ≥ 50 mL/min for subjects with creatinine levels > 1.5 x institutional ULN.
	  • Aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase ≤ 2.5 x ULN, or in subjects with liver metastases ≤ 5 x ULN.
	  • Total bilirubin ≤ 1.5 x ULN
	  • Subjects with hyperbilirubinemia clinically consistent with an inherited disorder of bilirubin metabolism (e.g., Gilbert Syndrome) will be eligible at the discretion of the principal investigator.
	  • International normalized ratio (INR) or prothrombin time (PT) < 1.5x ULN unless subject is receiving anticoagulation therapy as long as PT or INR is

	within therapeutic range of intended use of anticoagulant. • Activated partial thromboplastin time (aPTT) < 1.5 x ULN unless subject is receiving anticoagulant therapy, as long as PTT is within therapeutic range of intended use of anticoagulants. • Presence of baseline measureable disease by RECIST v1.1 for solid tumors. • Subjects must agree to pre- and on-treatment tumor biopsies. Use of outside archived tumor tissue for a baseline biopsy is not permitted. An optional research biopsy at the time of progression will also be discussed with these patients, however, is not mandatory. Subjects in whom biopsy is technically not feasible or in whom would result in unacceptable risk, in the opinion of the investigator, may be exempted from the biopsy requirement with approval by the principal investigator. **Key Exclusion Criteria:** • Treatment with chemotherapy (not including Tyrosine Kinase Inhibitors) or radiotherapy within 4 weeks (6 weeks from nitrosoureas or mitomycin C), or treatment with monoclonal antibody therapy within 4 weeks prior to start of study treatment. **Note:** No minimum washout period is required for tyrosine kinase inhibitor therapy (eg, imatinib or sunitinib). • Patients must have recovered from adverse events (greater than grade 1) due to prior anticancer therapy, except for stable chronic toxicities such as alopecia. • Participation in any other clinical study with investigational drug received within 28 days or 5 half lives (whichever is longer) before first dose. • Subjects who have received prior anti-PD-1 or anti-PD-L1 antibody therapy, or an IDO inhibitor. Subjects who have received experimental vaccines or other immune therapies should be discussed with the principal investigator to confirm eligibility. • Subjects receiving immunosuppressive treatment, including chronic steroids (at a dose equivalent to > 10 mg/day of prednisone) within 14 days prior to first study treatment. Inhaled or topical steroids or systemic steroids (at dose ≤10 mg/day of prednisone) is permitted.

	• Subjects with any active or inactive autoimmune process (eg, rheumatoid arthritis, moderate or severe psoriasis, multiple sclerosis, inflammatory bowel disease). Exceptions include vitiligo, hypothyroidism controlled on hormone replacement, type I diabetes, grave's disease, adrenal insufficiency on stable replacement doses of steroids (prednisone ≤10 mg/day or equivalent), or with principal investigator approval.
	• Subjects with known active hepatitis B (HBV) or hepatitis C (HCV) infection as defined by the following: (Hepatitis screening studies are required (see section 13))
	  • Positive test for hepatitis B surface antigen
	  • Positive test for hepatitis C antibody and/ or hepatitis C quantitative viral load (Note: Subjects with a positive hepatitis C antibody and negative quantitative hepatitis C PCR viral load are eligible)
	• Subjects with a known history of HIV, including patients with controlled disease on anti-retroviral therapy. HIV testing is not required as part of screening for this study.
	• Subjects receiving MAO inhibitors within 21 days prior to study enrollment (epacadostat increases serotonin levels, theoretically increasing the risk of serotonin syndrome, although this has not been reported in any ongoing clinical studies to date).
	• Any history of serotonin syndrome (SS) after receiving 1 or more serotonergic drugs.
	• Current pregnancy or breast-feeding.
	• A diagnosis of another active malignancy with the following exceptions: basal or squamous cell carcinoma of the skin, in-situ carcinoma of the cervix, isolated elevation of prostate-specific antigen, indolent secondary malignancies not requiring active therapy, or with the approval of the principal investigator. Subjects with a completely treated prior malignancy and no evidence of disease for ≥ 2 years are eligible.

Study Product, Dose, Route, Regimen	• Pembrolizumab 200 mg (flat dose) intravenously on day 1 of a 21 day cycle. • Epacadostat 100 mg orally BID continuously.
Study schedule/ Procedures:	Subjects will have regularly scheduled study visits at the clinical site on Day 1 of every cycle (CXD1), where safety assessments, including laboratory assessments, vital signs, and physical examinations will be performed.

Response to treatment will be determined by CT scans of the chest, abdomen, and pelvis with contrast. The response rate evaluation for the primary endpoint will be determined using RECIST v1.1 criteria; however, clinical decision making may be made based on irRECIST criteria to allow treatment beyond initial progression (see section 15). Imaging will be performed at the following time points:

Baseline scan	Baseline scan within 4 weeks prior to first treatment
Weeks 1 – 24	Every 6 weeks +/- 1 week (at weeks 6, 12, 18, 24)
Weeks 25 – until disease progression	Every 12 weeks +/- 1 week (at weeks 36, 48, 60, 72, 84, 96, 108)
2 years	If subjects achieve ongoing disease control at 2 years, patients will be taken off study treatment and observed with imaging every 12 weeks +/- 2 weeks. If the patient develops disease progression, the option of reinitiating study therapy may be considered.

Subjects will continue treatment until confirmed radiographic disease progression, intolerable toxicity or side effects or ongoing disease control at 2 years. In the latter case, imaging will be performed every 12 weeks, and should the patient develop evidence of disease progression, the option to reinitiate therapy may be discussed with the principal investigator.

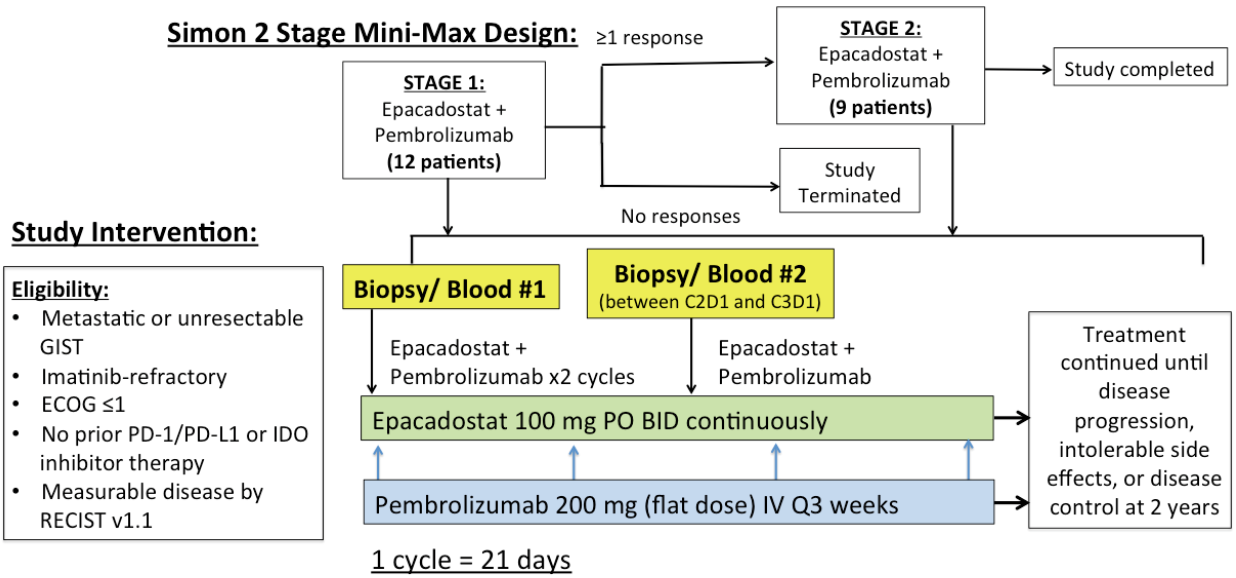
All patients must undergo paired biopsies for correlative studies. Biopsies will be collected at baseline and between C2D1 and C3D1 of therapy for correlative studies. An optional research biopsy at the time of progression will also be discussed with these patients, however, is not mandatory. Subjects in whom biopsy is technically not feasible or in whom would result in unacceptable risk, in the opinion of the investigator, may be exempted from the biopsy requirement with discussion with the principal investigator.

Adverse events and laboratory tests will be graded using the NCI CTCAE v4.0 scoring system. Adverse events will be assessed

	continuously during the study and for **90 days** after the last dose of treatment. Subjects will be followed until all treatment related adverse events have recovered to baseline or are deemed irreversible by the investigator. Subjects who are removed from study for reasons other than progression of disease will be followed every 3 months with imaging to evaluate disease status and survival analysis while the study remains open.
Duration of administration	Continuous treatment, on 21 day cycles. Treatment will be continued until confirmed radiographic disease progression, intolerable side effects, or ongoing response at 2 years of therapy.
Reference therapy	The reference therapy is salvage TKI therapy (sunitinib or regorafenib) in imatinib-refractory GIST patients, which has previously shown response rates of 7% and 5%, respectively.
Statistical Methodology	**Definition of primary outcome/endpoint:** The primary endpoint is the overall response rate as defined as the best response, confirmed at ≥4 weeks, within the first 24 weeks of the start of study therapy, using RECIST v1.1 criteria. **Definition of secondary outcomes/endpoints:** PFS is defined as time from registration to time of clinical or radiographic disease progression as defined by RECIST v1.1 criteria, or death. OS is defined as time from registration to time of death from any cause. **Analytic plan for primary objective:** We will estimate the response rate to combination therapy with epacadostat and pembrolizumab using the exact 95% confidence interval based on the binomial distribution. **Analytic plan for secondary and exploratory objectives:** • We will estimate the survival distribution for both PFS and OS endpoints using the Kaplan Meier method. The log rank test will be used to examine differences between survival curves. • For correlative studies we will apply either the Fisher's exact test or Wilcoxon rank sum test to examine the correlation between response status and markers for categorical and continuous variables, respectively.

	Sample size justification: We will use a Simon mini-max two-stage design with a target objective response rate of 20%, compared to a historical response rate of 5% with salvage tyrosine kinase inhibitor monotherapy, and the probabilities of type I and type II error set at 0.1 and 0.2 respectively. In the first stage, 12 patients will be accrued. If less than 1 patient achieves a response among the initial 12 patients, the study will be declared negative and terminated. If at least 1 patient achieves a response, an additional 9 patients will be accrued to the second stage for a total of 21 evaluable patients. If at least 3 total patients achieve a response, that treatment will be declared positive for attaining the primary endpoint. This study design yields at least 80% power to detect a 20% response rate (compared to the null hypothesis of 5%) at a significance level of 10%. There is a 54% chance of stopping at Stage 1 if the true confirmed response rate is at most 5% (null hypothesis). Accounting for 10% dropout, we will plan to enroll a total of 23 patients.

Protocol Schema:



Schedule of CT scan assessments	
Baseline	Baseline
Weeks 1-24	Every 6 weeks +/- 1 week
Weeks 25 – 2 years	Every 12 weeks +/- 1 week

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1. INTRODUCTION

While targeted therapy with imatinib has significantly improved survival for patients with inoperable and metastatic gastrointestinal stromal tumors (GIST), the majority will eventually progress after a median of 20-26 months. Standard second-line treatment with sunitinib has a response rate of 7%, and third-line treatment with regorafenib has a response rate of only 5%. More effective treatments for imatinib-refractory GIST are needed. There is pre-clinical and clinical evidence that the anti-tumor mechanism of KIT inhibition in GIST is partially mediated by effects on the immune system. Indoleamine 2,3-dioxygenase (IDO) is an enzyme that metabolizes tryptophan to immunosuppressive metabolites that suppress cytotoxic T effector cells and activate inhibitory T regulatory cells. In a GIST mouse model, KIT inhibition with imatinib alters the tumor immune microenvironment by inhibiting IDO. Further, imatinib enhances the effect of anti-CTLA-4 and anti-PD-1 therapy in mice. We have also observed clinical benefit in refractory GIST patients treated on our ongoing phase I trial of dasatinib and ipilimumab. This data suggests that inhibition of IDO may be an important anti-tumor mechanism in GIST and can be combined with checkpoint inhibition to potentiate tumor control.

This is a single-arm Phase II study to assess the efficacy of combined IDO and PD-1 inhibition with epacadostat (IDO inhibitor) and pembrolizumab (anti-PD-1 antibody) in patients with imatinib-refractory GIST (target enrollment of 23 subjects), with a primary endpoint of overall response rate using RECIST v1.1 criteria. We hypothesize that treatment with epacadostat and pembrolizumab will increase the response rate compared to what has been historically achieved with salvage tyrosine kinase inhibitors. Baseline and on-treatment biopsies will be obtained in a total of 10 subjects, with the goal of characterizing the effects of combined IDO and PD-1 inhibition on the tumor immune microenvironment.

2. STUDY OBJECTIVES

2.1 Primary Objective(s):

- To assess the efficacy of combined IDO and PD-1 inhibition in a single arm phase II trial of epacadostat and pembrolizumab in patients with advanced imatinib-refractory GIST, using a primary endpoint of overall response rate using RECIST v1.1 criteria.

2.2 Secondary Objective(s):

- To evaluate the progression free survival (PFS) of patients with advanced GIST treated with epacadostat and pembrolizumab using RECIST v1.1 criteria.
- To evaluate the overall survival (OS) of patients with advanced GIST treated with epacadostat and pembrolizumab.
- To evaluate response rate using Choi criteria.
- To evaluate the safety and tolerability of combined epacadostat and pembrolizumab treatment in the advanced GIST population.

2.3 Exploratory Objectives:

- To correlate the effect of IDO inhibition with response to therapy by evaluating baseline and on-treatment serum samples for tryptophan metabolite levels. We predict that greater inhibition of IDO activity with epacadostat, as measured by a decrease in the serum kynurenine to tryptophan ratio, will correlate with treatment response.
- To characterize the effect of combined therapy with IDO and PD-1 inhibition on T-cell subsets by evaluating baseline and on-treatment tumor samples for changes in the T-effector to T-regulator cell ratio using immunohistochemistry. We predict that treatment with epacadostat and pembrolizumab will result in a higher ratio of T effector to T regulatory cells.
- To characterize the relationship between PD-L1 status and response to combined IDO and PD-1 inhibition.

3. BACKGROUND

3.1 Gastrointestinal Stromal Tumors (GIST)

Background on GIST:
Gastrointestinal stromal tumors (GIST) are the most common sarcomas of the digestive tract, with approximately 4,000 to 6,000 new cases diagnosed each year in the United States.[1] The majority of these tumors harbor activating KIT or PDGFR-alpha mutations, making them sensitive to targeted treatment with the tyrosine kinase inhibitor imatinib mesylate.[2] Imatinib has activity against KIT and PDGFR, and is considered first line therapy for non-operable and metastatic GIST. Treatment with imatinib in GIST leads to disease control in 70-85% of patients (overall response rate of 68.1%, and stable disease in 15.6%), with a median progression free survival (PFS) of 20-26 months.[3-6] While targeted therapy with imatinib has significantly improved survival for patients with advanced GIST, about 14% of patients exhibit primary resistance to imatinib.[4] In addition, the majority of patients will eventually acquire mutations in KIT or PDGFR leading to secondary resistance after an average of 2 years of initial imatinib therapy.[7-9]

Treatment for imatinib-refractory advanced GIST:
Effective treatment options for patients with imatinib-refractory GIST are limited. Sunitinib, an oral receptor tyrosine kinase inhibitor with activity against KIT, PDGFR, as well as VEGF receptors, FLT3, and RET, has been shown to improve progression free survival in patients with inoperable GIST who have failed imatinib therapy, and is now considered standard second-line treatment for advanced GIST. In a phase III randomized placebo-controlled study of sunitinib versus placebo in patients with imatinib-resistant advanced GIST, the sunitinib group had an overall median progression free survival of 27.3 weeks compared to 6.4 weeks in the placebo group.[10] However, the overall response rate was only 7 percent in the sunitinib treated group, compared with 0 percent in the placebo group.[10] Regorafenib, an oral multikinase inhibitor of KIT, PDGFR, VEGFR, RET, BRAF, and FGFR, has been studied as third line treatment in imatinib and sunitinib refractory patients, and has been shown to improve progression free survival from

0.9 months to 4.8 months ($p < 0.0001$), with an overall response rate of 4.5 percent.[11] Given the overall low response rates to TKI therapy in the second-line setting and beyond, more effective therapies for imatinib-refractory GIST patients are needed.

Other TKIs with preclinical activity against KIT and PDGFR have been examined as potential therapeutic options both in front-line and refractory GIST. Dasatinib is a TKI with a spectrum of activity including the SRC family of kinases in addition to KIT and PDGFR that has been evaluated as a treatment option for GIST. Preclinical data has described activity of dasatinib toward mutant KIT,[12] as well as anti-tumor efficacy in imatinib-resistant GIST cell lines.[13] Trent and colleagues presented the results of a phase II study of dasatinib as third-line therapy for GIST at ASCO 2011.[14] Results included a Choi partial response rate of 32%, a median PFS of 2 months and median OS of 19 months, and a PFS rate of 21% at 6 months.

In summary, although treatment of GIST with tyrosine kinase inhibitors results in demonstrated clinical benefit, this efficacy is not sustained and treatment with KIT inhibition does not result in the cure of patients with advanced disease. Given the overall low response rates to TKI therapy in the second-line setting and beyond, novel and more effective therapies for imatinib-refractory GIST are needed.

3.2 The immune system is an important anti-tumor mechanism in GIST

Anti-tumor effects of imatinib are mediated by the immune system:
While current treatment for imatinib-refractory GIST has focused on targeted therapy with newer generation TKIs, there is pre-clinical and clinical evidence that the anti-tumor effects of KIT inhibition in GIST are also mediated by effects on the immune system. In a mouse model of KIT mutant ($KIT^{V558/+}$) GIST, the response to imatinib was dependent upon the presence of intact CD8+ T cells—depletion of CD8+ T cells with a monoclonal antibody inhibited the response to imatinib, and GIST $Rag1^{-/-}$ mice, which lack mature T and B cells, had larger tumors than age matched controls or GIST-$\mu MT^{-/-}$ mice, which lack only B cells.[15] Imatinib treatment also increased the number and activation of intratumoral CD8+ T_{eff} cells and induced apoptosis of T_{reg} cells in these mice.[15] In human GIST tumors, the ratio of T_{eff} cells to T_{reg} cells was also shown to correlate with imatinib sensitivity.[15]

3.3 Indoleamine 2,3-dioxygenase (IDO) as a target for cancer therapy

Indoleamine 2,3-dioxygenase (IDO) in cancer:
Indoleamine 2,3-dioxygenase (IDO) is a heme-containing, monomeric oxidoreductase produced in tumor cells, macrophages, and dendritic cells, that metabolizes tryptophan to N-formyl-kynurenine metabolites.[16-19] IDO driven oxidation of tryptophan results in a strong inhibitory effect on the development of T-cell−mediated responses by blocking T-cell activation and inducing T-cell apoptosis.[20] IDO activity also promotes the differentiation of naive T cells to T regulatory cells (T_{reg} cells), which has been shown to promote tumor growth.[19]

A critical role for IDO in immunomodulation has been confirmed in animal models, including models of allograft tolerance, inflammation, and cancer.[21] While IDO inhibition can exacerbate

disease in models of autoimmune disorders, IDO null mice show no evidence of susceptibility to developing spontaneous autoimmunity or alterations in immune system development, suggesting the therapeutic potential of IDO inhibition.[21] Within the context of cancer, several groups have demonstrated that blockade of IDO activity can directly influence the ability of tumor-bearing animals to reject tumors. Studies with the IDO inhibitor, 1-methyl-tryptophan, demonstrate that IDO inhibition can increase the efficacy of various chemotherapeutic agents without increased toxicity.[18,22] In addition, IDO activity, as measured by levels of serum tryptophan and kynurenine, appears to be chronically activated in subjects with cancer and correlates with more extensive disease. IDO has been found to be overexpressed by a wide variety of human tumor cell types as well as by the DCs that localize to the tumor-draining lymph nodes.[18] Increased expression of IDO in tumor cells has been shown to be an independent prognostic variable for reduced overall survival in various tumors including melanoma, ovarian cancer, and colorectal.[17,23,24]

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

Rationale for combined IDO and PD-1 inhibition in cancer:
Blockade of immune inhibitory pathways with CTLA-4 or PD-1/PD-L1 blockade is emerging as an important therapeutic modality for the treatment of cancer. Although these single agents have antitumor activity, multiple immune inhibitory mechanisms are present concurrently within the tumor microenvironment, suggesting that combination therapies may be required for optimal therapeutic effect. As IDO is another negative regulatory mechanism that contributes to tumor-derived immune suppression, targeting of both IDO and immune checkpoints may lead to enhanced efficacy. In preclinical models, IDO inhibition has been shown to synergize with blockade of either anti−CTLA-4 or anti−PD-1/PD-L1 in delaying tumor growth and increasing overall survival. In a mouse model of melanoma, combined IDO and CTLA-4 and PD-1 inhibition resulted in synergistic anti-tumor effect.[25] Currently there is an ongoing phase 1/2 clinical trial of epacadostat in combination with pembrolizumab in advanced solid tumors (NCT 02178722). The Phase 1 portion of the study has been completed and the recommended phase II dose of pembrolizumab has been determined.

3.4 Rationale for combined IDO and PD-1 inhibition in GIST.

KIT inhibition alters the tumor immune microenvironment via IDO inhibition in GIST: Studies in a GIST mouse model found that imatinib altered intratumoral T cells through inhibition of IDO. In this GIST mouse model, KIT induced expression of the transcription factor ETV4 that transactivated IDO. Treatment with imatinib was able to inhibit this interaction.[15] Treatment with the IDO specific inhibitor 1-methyl-D-tryptophan (1-MT) lead to a decrease in tumor size accompanied by an increase in intratumoral T_{eff} cells in mice. Evaluation of human GIST tumor specimens was consistent with the findings in the GIST mouse model and demonstrated IDO suppression and a higher ratio of intratumoral T_{eff} to T_{reg} cells in imatinib-sensitive compared with imatinib-resistant tumors.[15]

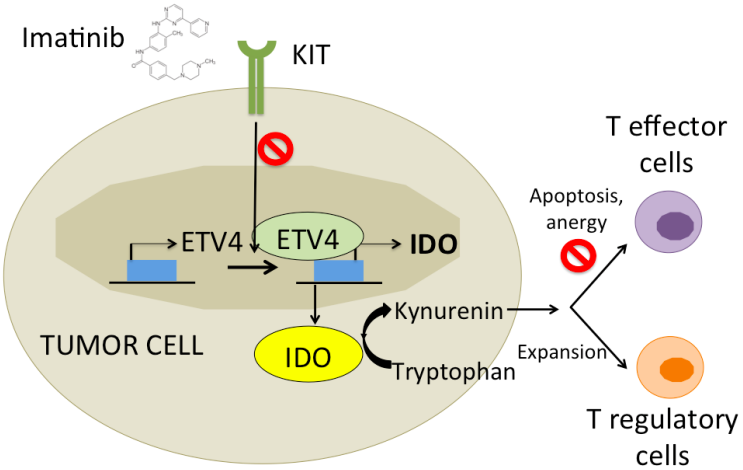

Figure 1. Imatinib inhibits IDO and alters the tumor immune microenvironment in GIST tumors.

PD-L1 is expressed in GIST:
It has been previously demonstrated that GIST tumors express PD-L1. 29% of GIST tumors expressed PD-L1 by immunohistochemistry, which was the highest prevalence observed amongst all sarcoma pathologies evaluated in one study.[26] Tumor lymphocyte and macrophage infiltration was present in 100% of these specimens, and PD-L1 was expressed in 50% of tumor infiltrating lymphocytes and macrophages.[26] Other studies have shown that CD3+ tumor infiltrating lymphocytes are present in GIST and predict improved progression free survival.[27] Given the high rate of PD-L1 expression, evaluation of anti-PD1/PD-L1 agents in GIST tumors is of high priority.

KIT inhibition combined with immunotherapy enhances anti-tumor effect in pre-clinical studies and a Phase I study:

a. KIT + CTLA-4 inhibition: In a GIST mouse model, CTLA-4 blockade synergized with imatinib to reduce tumor growth (Figure 2).[15] We have also previously demonstrated clinical benefit with the combination of dasatinib and ipilimumab in a heavily pretreated GIST population (mean of 4.5 prior treatments) enrolled on a phase I trial of dasatinib and ipilimumab. In the interim analysis, of 8 GIST patients enrolled, 3 achieved disease stability following initial tumor progression by RECIST criteria, with response kinetics similar to that described with ipilimumab immunotherapy in melanoma. One patient had a durable response with stable disease for over 1 year (Figure 3).[28] The full results of this study were recently reported, with a total of 28 patients enrolled, including 20 patients with a diagnosis of GIST and 8 patients with other sarcomas. Dose limiting toxicities observed in this Phase I study included grade 3 gastric hemorrhage in 1 patient and grade 3 anemia in 2 patients. The final MTD was established as dasatinib at 140 mg daily and ipilimumab at 3 mg/kg. There were no partial or complete responses observed by RECIST or irRC; however, there were 7 patients (out of 13 evaluable GIST patients) with partial responses by Choi criteria. In addition, 3 (out of 13 evaluable GIST patients) achieved stable disease.[29]

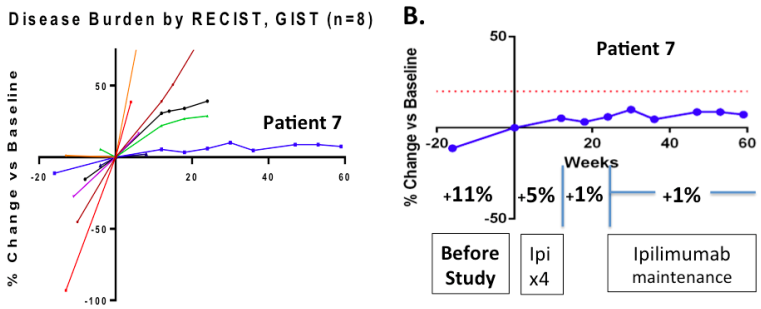

Figure 2. Response by RECIST criteria in refractory GIST patients treated on a Phase I trial of dasatinib and ipilimumab. (A) Disease stability was observed in 3 out of 8 patients. (B) Long-term disease stability achieved in a GIST patient (% represents rate of change in tumor burden by RECIST criteria).

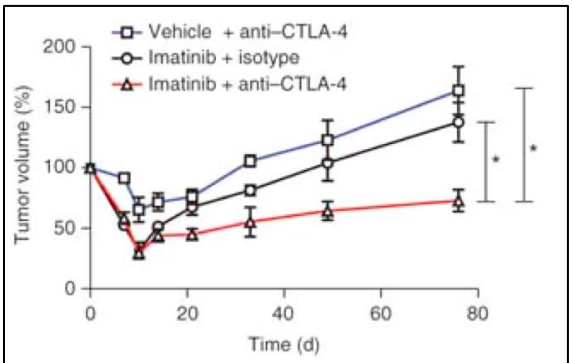

FIGURE 3. Combined CTLA-4 blockade and imatinib in a GIST mouse model is synergistic and inhibits tumor growth.[15]

b. KIT + PD-1/PD-L1 inhibition: In a GIST mouse model, combined PD-1 or PD-L1 blockade with imatinib was more effective than imatinib therapy alone. Mice treated with either PD-1 or PD-L1 antibodies in combination with imatinib had an additional 25% or 30% decrease in tumor weight respectively.[30,31] This combination resulted in decreased phosphorylated KIT, phosphorylated STAT1, TGF-β, and IDO protein expression (Figure 4), as well as decreased IDO mRNA expression. The anti-tumor effect of combined imatinib and anti-PD-1 therapy was durable at 3 months in this GIST mouse model.[30]

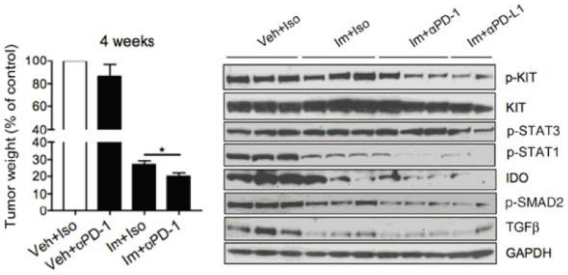

Figure 4. Tumor weights from *KIT*$^{V558\Delta/+}$ mice (3-5 per group) treated with vehicle, imatinib (Im), or Im + anti-PD-1/PD-L1 antibody for 4 weeks (left). Western blot analysis (right) of these tumors shows decrease in phosphorylated KIT, phosphorylated STAT1, TGF-β, and IDO with combination treatment. [30]

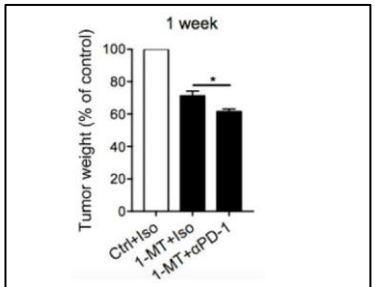

Figure 5. Tumor weight (% of control) of *KIT*$^{V558\Delta/+}$ mice (3-5 per group) treated with 1-MT (IDO inhibitor) +/- anti-PD-1 antibody for 1 week. Additional decrease in tumor weight was seen with combined IDO and PD-1 inhibition at 1 week.[30]

IDO inhibition combined with PD-1/PD-L1 blockade enhances anti-tumor effect in a GIST mouse model:

IDO inhibition with 1-MT was combined with PD-1/PD-L1 axis blockade in a GIST *KIT*$^{V558\Delta/+}$ mouse model. After 1 week of combined treatment, additional decrease in tumor weight was observed compared to IDO inhibition alone or controls (Figure 5).[30]

Rationale and Hypothesis:

New approaches to the treatment of imatinib-refractory GIST are needed. Investigation of the combination of IDO and PD-1 inhibition in GIST patients is warranted for the following reasons:

- Pre-clinical evidence has shown that KIT inhibition alters the tumor immune microenvironment by increasing T_{eff} cells and decreasing T_{reg} cells via suppression of the IDO enzyme.
- PD-L1 is expressed in a high proportion of GIST tumors compared with other sarcoma sub-types, making investigation of anti-PD-1/PD-L1 agents a high priority in GIST.
- Combined KIT and PD-1 or CTLA-4 inhibition was synergistic in a GIST mouse model, and we have observed clinical benefit in our phase I trial of dasatinib and ipilimumab in GIST.

We propose a phase II trial of epacadostat and pembrolizumab to evaluate the efficacy of combined IDO and PD-1 inhibition in imatinib-refractory advanced GIST patients. We hypothesize that patients treated with IDO and PD-1 inhibition will have improved objective response rates compared to historical controls treated with salvage TKI therapy.

4. INVESTIGATIONAL AGENT: EPACADOSTAT (INCB24360)

4.1 Preclinical Data

Epacadostat is a novel selective inhibitor of indoleamine 2,3-dioxygenase 1 (IDO1) manufactured by Incyte corporation. In cell-based assays, epacadostat potently inhibits IDO in both human tumor cells and human dendritic cells resulting in reduced tryptophan to kynurenin conversion (IC_{50} values = 7.1-12.7 nM), and does not significantly inhibit other proteins that could impact

tryptophan catabolism.

To test whether epacadostat could reverse the inhibitory effect of IDO1 on T cells, IDO1+ DCs were cocultured with either CD4+ or CD8+ T cells in the presence of a soluble anti-CD3 antibody to promote T-cell activation and growth. Compared with the T cells cocultured with immature DCs, which do not express IDO1, 3H-thymidine incorporation in CD4+ or CD8+ T cells was significantly suppressed when they were cocultured with DCs, which express high levels of IDO1. Addition of epacadostat to the cocultures protected CD4+ or CD8+ T cells from this inhibitory effect. The effects of epacadostat in this system were dose-dependent and were consistent with the potency of the compound in blocking Trp conversion, with an EC50 value of 17.7 ± 4.7 nM (n = 3). In these same cultures, the effect of INCB24360 on cytokine levels was examined. Epacadostat treatment led to a 5-fold increase in the IFN-γ levels produced by CD4+ and CD8+ T cells when compared with vehicle control. Like T cells, NK cell proliferation was also inhibited by IDO1-mediated Trp catabolism, and epacadostat treatment reversed this, resulting in a 4- to 5-fold increase in 3H-thymidine uptake by NK cells.

Recent studies have also shown the potential for IDO1 activity to promote the differentiation of naïve T cells to cells with a regulatory T phenotype (Treg). The ability of IDO1+ DCs to promote differentiation to Treg cells as well as the ability of epacadostat to reverse this effect was therefore examined in an *in vitro* culture system similar to those previously reported. In these studies, co-culture of naïve CD4+CD25- T cells with IDO1+ DCs resulted in a 2-fold increase in Treg cells as defined by Foxp3 staining when the cells were cultured with interleukin (IL)-2. Inclusion of epacadostat in the cultures reversed this effect.

In Vitro Activity of Epacadostat on Human Immune Cells

Cell Type	Effects of IDO1	Epacadostat Effects
T cells	Decreased proliferation	Enhanced proliferation; enhanced IFN-gamma production
NK cells	Decreased proliferation	Enhanced proliferation
T_{reg}	Increased cell numbers	Decreased cell numbers
DC	Increased apoptosis	Decreased apoptosis; increased DC activation markers

4.2 Clinical Data to Date

As of October 2016, a 12 Incyte-sponsored clinical studies have been completed or are ongoing. Epacadostat was evaluated in a multi-center, dose-escalation Phase 1 study (INCB 24360-101) in subjects with refractory solid tumors using a 3 + 3 design to determine the safety and tolerability, PK, and pharmacodynamics of escalating oral doses of epacadostat. Epacadostat was well tolerated at doses up to 700 mg BID. Fatigue and nausea were the most frequently reported treatment-related treatment-emergent adverse event (48.1%, 25 subjects). Two DLTs occurred, including 1 DLT for radiation pneumonitis and 1 DLT for fatigue. An MTD was not determined..

There is an ongoing Phase I/II study of the safety, tolerability, and efficacy of pembrolizumab in

combination with epacadostat in subjects with selected solid tumors, followed by an open-label expansion in subjects with select tumors (INCB 24360-202). This study enrolled 22 subjects with advanced melanoma on the Phase I portion of the study, of which 19 were treatment naïve. The overall response rate was 58% (11 of 19 patients), with 26% achieving a complete response and 32% achieving a partial response. 3 patients (16%) had stable disease and 14 patients (74%) achieved disease control.[32] Responses were observed in all epacadostat dose cohorts greater than or equal to 50 mg BID and at all sites of target lesions. Responses were also observed in patients with previously treated advanced melanoma (1 complete response, 1 stable disease, n=3), non-small cell lung cancer (5 partial responses, 2 stable disease, n=12), renal cell carcinoma (3 partial responses, 5 stable disease, n=11), endometrial adenocarcinoma (1 complete response, 1 partial response, n=7), transitional cell carcinoma (3 partial responses, n=5), triple negative breast cancer (2 stable disease, n=3), and head and neck squamous cell carcinoma (1 partial response, 1 stable disease, n=2).[32]

The safety profile for the 300mg BID dose of epacadostat in combination with pembrolizumab in the Phase I/II study (INCB24360-202) did not exceed the MTD in that study. While there was a higher incidence of grade 3 rash in the 300mg BID cohort compared to the 100mg BID cohort, these did not qualify as protocol-specified DLTs. The dose combination of 100mg BID of epacadostat plus pembrolizumab is currently being evaluated in a Phase III melanoma study (INCB24360-301). The epacadostat 100mg BID dose combination is being moved forward as the recommended dose in combination with pembrolizumab because of the lower incidence of dose interruptions and dose reductions compared to the 300mg BID dose.

4.3 Other Agent(s): Pembrolizumab

Pharmaceutical and Therapeutic Background

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

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). The structure of murine PD-1 has been resolved. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling

motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda™ (pembrolizumab) has recently been approved in the United Stated for the treatment of patients with unresectable or metastatic melanoma, patients with metastatic NSCLC whose tumors have high PD-L1 expression [(Tumor Proportion Score (TPS) ≥50%)] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, and no prior systemic chemotherapy treatment for metastatic NSCLC, patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving. Approval was also received for patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.

Recently, pembrolizumab received accelerated approval for treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, as well as patients with MSI-H or dMMR colorectal cancer following progression on a fluoropyrimidine, oxaliplatin, and irinotecan.

Preclinical and Clinical Trial Data

Refer to the Investigator's Brochure for Preclinical and Clinical data.

Rationale for Dose Selection/ Regimen/ Modification

An open-label Phase I trial (Protocol 001) is being conducted to evaluate the safety and clinical activity of single agent MK-3475. 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 MK-3475 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. Recent data from other clinical studies within the MK-3475 program has shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of MK-3475 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 MK-3475 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. MK-3475 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 MK-3475 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.

The rationale for further exploration of 2 mg/kg and comparable doses of pembrolizumab in solid tumors is based on: 1) similar efficacy and safety of pembrolizumab when dosed at either 2 mg/kg or 10 mg/kg Q3W in melanoma patients, 2) the flat exposure-response relationships of pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W, 3) the lack of effect of tumor burden or indication on distribution behavior of pembrolizumab (as assessed by the population PK model) and 4) the assumption that the dynamics of pembrolizumab target engagement will not vary meaningfully with tumor type.

The choice of the 200 mg Q3W as an appropriate dose for the switch to fixed dosing is based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe.

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

5. STUDY DESIGN

5.1 General study design

This is a single-arm Phase 2 study to evaluate the efficacy of combined epacadostat and pembrolizumab in advanced imatinib-refractory GIST patients.

Study Intervention: All subjects will receive pembrolizumab 200 mg IV every 3 weeks and epacadostat 100 mg PO BID continuously.

Schedule of Evaluations: Subjects will have regularly scheduled study visits at the clinical site on Day 1 of every cycle (CXD1), where safety assessments, including laboratory assessments, vital signs, and physical examinations will be performed (see Section 12 for detailed study evaluations, and Section 13 for study calendar).

Response to treatment will be determined by CT scans of the chest, abdomen, and pelvis with contrast. The overall response rate for the primary endpoint evaluation will be determined by RECIST v1.1 criteria; however, clinical decision making may be made based on immune related RECIST (irRECIST) criteria to allow treatment beyond initial progression (see section 15). In patients who are unable to get a CT scan w/ contrast due to renal function (or any other reason), an MRI with and without contrast may be used instead. Imaging will be performed at the following time points:

Baseline scan	Baseline scan within 4 weeks prior to first treatment
Weeks 1 – 24	Every 6 weeks +/- 1 week (at weeks 6, 12, 18, 24)
Weeks 25 – until disease progression	Every 12 weeks +/- 1 week (at weeks 36, 48, 60, 72, 84, 96, 108)
2 years	If subjects achieve ongoing disease control at 2 years, patients will be taken off study treatment and observed with imaging every 12 weeks +/- 2 weeks. If the patient develops disease progression, the option of reinitiating study therapy may be considered.

Duration of treatment: Subjects will continue treatment until confirmed radiographic disease progression, intolerable toxicity or side effects (see Section 6.6 for Criteria for Withdrawal) or ongoing disease control at 2 years. In the latter case, imaging will be performed every 12 weeks, and should the patient develop evidence of disease progression, the option of reinitiating study therapy may be considered based upon discussion with the study principal investigator.

Biopsies for correlative studies: All enrolled subjects must undergo paired biopsies for correlative studies. CT-guided biopsies will be collected at baseline and between C2D1 and C3D1 of therapy for correlative studies. An optional biopsy for research purposes at the time of progression will also be discussed with these patients, however, is not mandatory. Subjects in whom biopsy is technically not feasible or in whom would result in unacceptable risk, in the opinion of the investigator, may be exempted from the biopsy requirement with discussion with the principal investigator.

Duration of follow-up: Adverse events and laboratory tests will be graded using the NCI CTCAE v4.0 scoring system. Adverse events will be assessed continuously during the study and for **90 days** after the last dose of treatment. Subjects will be followed for at least **90 days** post-study, or until all treatment related adverse events have recovered to baseline or are deemed irreversible by the investigator. Subjects who are removed from study for reasons other than progression of disease will be followed every 3 months with imaging to evaluate disease status and survival analysis while the study remains open.

5.2. Number of subjects

Using a Simon two-stage design, 12 patients will be treated initially. If an objective response is observed in at least 1 patient, we will proceed with enrollment of an additional 9 patients for a total of 21 evaluable patients. Assuming a 10% drop-out rate, we anticipate a total maximal accrual of 23 patients.

6. SUBJECTS SELECTION AND WITHDRAWAL

6.1. Inclusion Criteria

The following criteria are required for inclusion in the study:

1. Histologically confirmed diagnosis of GIST.

2. Unresectable or metastatic GIST.

3. Allowable prior therapies:

a. Subjects must have had clinical or radiographic progression on imatinib. Those who were taken off of imatinib for intolerance must have progressed on at least one other TKI.
b. Subjects must have received ≥ 1 prior systemic therapy (including imatinib). A maximum of 4 prior therapies for metastatic disease are allowed.

4. Male or female subjects, age 18 years or older.

5. ECOG performance status ≤ 1 (Appendix A)

6. Life expectance of ≥ 3 months.

7. Laboratory parameters within the following Protocol-defined range. All screening laboratory tests should be performed within 28 days of treatment initiation and must be independent of hematopoietic growth factor support.
   - Absolute neutrophil count ≥ 1.5 x 10^9/L.
   - Platelets ≥ 100 x 10^9/L.
   - Hemoglobin ≥ 9 g/dL (transfusion is acceptable to meet this criteria)
   - Serum creatinine ≤ 1.5 x institutional upper limit of normal (ULN) OR calculated creatinine clearance ≥ 50 mL/min for subjects with creatinine levels > 1.5 x institutional ULN.
   - Aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase ≤ 2.5 x ULN, or ≤ 5 x ULN in subjects with liver metastases.
   - Total bilirubin ≤ 1.5 x ULN
     - **Note**: patients with hyperbilirubinemia clinically consistent with an inherited disorder of bilirubin metabolism (eg, Gilbert syndrome) will be eligible at the discretion of the principal investigator.
   - International normalized ratio (INR) or prothrombin time (PT) < 1.5x ULN unless subject is receiving anticoagulation therapy as long as PT or INR is within therapeutic range of intended use of anticoagulant.
   - Activated partial thromboplastin time (aPTT) < 1.5 x ULN unless subject is receiving anticoagulant therapy, as long as PTT is within therapeutic range of intended use of anticoagulants.

8. Presence of baseline measureable disease by RECIST v1.1 for solid tumors, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥ 20 mm with conventional techniques or as ≥ 10 mm with spiral CT scan, MRI, or calipers by clinical exam. (See Section 15.4 for the evaluation of measurable disease).

9. The effects of pembrolizumab and epacadostat on the developing human fetus are unknown, and thus female subjects of childbearing potential (defined as women who have not undergone surgical sterilization with a hysterectomy and/or bilateral oophorectomy, and are not postmenopausal (defined as ≥ 12 months of amenorrhea)) must have a negative pregnancy test at screening and must agree to use adequate contraception (complete

abstinence, or two methods of birth control (Appendix B)) prior to study entry and until at least 4 months after the last dose of study treatment. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

10. Fertile men must also agree to use adequate contraception (2 barrier methods or abstinence) during the study and for up to 4 months after the last dose of study drug.

11. All subjects must agree to pre- and on-treatment tumor biopsies. Subjects in whom biopsy is technically not feasible or in whom would result in unacceptable risk, in the opinion of the investigator, may be exempted from the biopsy requirement with discussion with the principal investigator. Use of outside archived tumor tissue for a baseline biopsy is not permitted.

12. Willingness and ability to provide written informed consent prior to any study-related procedures and to comply with all study requirements.

6.2. Exclusion Criteria

1. Treatment with chemotherapy (not including Tyrosine Kinase Inhibitors) or radiotherapy within 4 weeks (6 weeks from nitrosoureas or mitomycin C), or treatment with monoclonal antibody therapy within 4 weeks prior to start of study treatment.

   Note: No minimum washout period is required for tyrosine kinase inhibitor therapy (eg, imatinib or sunitinib).

2. Patients must have recovered from adverse events (greater than grade 1) due to prior anticancer therapy, except for stable chronic toxicities such as alopecia.

3. Participation in any other clinical study with investigational drug received within 28 days or 5 half lives (whichever is longer) before first dose.

4. Subjects who have received prior anti-PD-1 or anti-PD-L1 antibody, or an IDO inhibitor. Subjects who have received experimental vaccines or other immune therapies should be discussed with the principal investigator to confirm eligibility.

5. Any prior ≥ Grade 3 immune-related adverse event (irAE) while receiving immunotherapy, or any unresolved irAE > grade 1.

6. Subjects receiving immunologically based treatment for any reason, including chronic steroids or prednisone (at dose >10 mg/day of prednisone) within 14 day prior to first study treatment. Inhaled or topical steroids or systemic steroids (at dose ≤10 mg/day of prednisone) is permitted.

7. Subjects with any active or inactive autoimmune process (eg, rheumatoid arthritis, moderate or severe psoriasis, multiple sclerosis, inflammatory bowel disease) or who are receiving systemic therapy for an autoimmune disease. Exceptions include vitiligo, hypothyroidism controlled on hormone replacement, type I diabetes, Grave's disease, adrenal insufficiency on stable replacement doses of steroids (prednisone ≤10 mg/day or equivalent), or with principal investigator approval.

8. No prior organ allograft or allogenic bone marrow transplantation.

9. History of (noninfectious) pneumonitis that require steroids or current pneumonitis.

10. A diagnosis of another active malignancy with the following exceptions: basal or squamous cell carcinoma of the skin, in-situ carcinoma of the cervix, isolated elevation of prostate-specific antigen, indolent secondary malignancies not requiring active therapy, or with the approval of the principal investigator. Subjects with a completely treated prior malignancy and no evidence of disease for ≥ 2 years are eligible.

11. Subjects with known active hepatitis B (HBV) or hepatitis C (HCV) infection as defined by the following (Hepatitis screening studies are required (see section 13)):
    - Positive test for hepatitis B surface antigen
    - Positive test for hepatitis C antibody and/ or hepatitis C quantitative viral load (Note: Subjects with a positive hepatitis C antibody and negative quantitative hepatitis C PCR viral load are eligible)

12. Subjects with a known history of HIV, including patients with controlled disease on anti-retroviral therapy. HIV testing is not required as part of screening for this study.

13. Subjects receiving MAO inhibitors within 21 days of study enrollment (epacadostat increases serotonin levels, theoretically increasing the risk of serotonin syndrome, although this has not been reported in any ongoing clinical studies to date).

14. Any history of serotonin syndrome (SS) after receiving 1 or more serotonergic drugs.

15. Current pregnancy or breast feeding. Pregnant women are excluded from this study because the teratogenicity of epacadostat and pembrolizumab are unknown. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with pembrolizumab and/or epacadostat, breastfeeding should be discontinued in all female subjects.

16. Receipt of live attenuated vaccines (including, but not limited to: intranasal influenza vaccine (FluMist), measles, mumps, rubella, chicken pox, yellow fever, rabies, Bacillus

Calmette-Guerin (BCG), and typhoid vaccine) within 30 days before the first dose of study treatment.

17. Concurrent use of any medication that is an inhibitor of UGT1A9 (section 8.3.2) during the screening or treatment period.

18. Major surgical procedure or significant traumatic injury within 14 days of initiating study drug or anticipation of the need for major surgery during the study.

19. Inability to swallow capsules, or refractory nausea and vomiting, malabsorption, an external biliary shunt, or significant bowel resection that would preclude adequate absorption.

20. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, active liver disease, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

21. History of current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, or interfere with the subject's participation for the full duration of the study.

22. Known allergy or reaction to any component of either study drug formulation.

6.3. Pregnancy

The effects of pembrolizumab and epacadostat on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (Appendix B) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 4 months after completion of pembrolizumab and/or epacadostat administration.

Sexually active women of child-bearing potential (WOCBP) must use an effective method of birth control during the course of the study, in a manner such that risk of failure is minimized (Appendix B).

Before study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during study participation and the potential risk factors for an unintentional pregnancy. The subject must sign an informed consent form documenting this discussion.

All WOCBP MUST have a negative pregnancy test at the time of study screening. The minimum

sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG. If the pregnancy test is positive, the subject must not receive treatment and must not be enrolled in the study.

In addition, all WOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for subject safety). The investigator must immediately notify the sponsor of this event and record the pregnancy on the Pregnancy Surveillance Form (not an SAE form). Initial information on a pregnancy must be reported immediately to the sponsor, and the outcome information provided once the outcome is known. Completed Pregnancy Surveillance Forms must be forwarded to Incyte and Merck according to SAE reporting procedures (See Section 10.4.4).

Any pregnancy that occurs in a female partner of a male study participant should be reported to the sponsor. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (e.g., X-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. In addition, the investigator must report and follow-up on information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants should be followed for a minimum of 8 weeks.

6.4. Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

6.5. Subject Recruitment

Patients will be recruited for the study from investigator or co-investigator clinical practices and referring physicians.

6.6. Early Withdrawal of Subjects

6.6.1. When and How to Withdraw Subjects

Patients may withdraw from study at any time. Patients who discontinue early should return within 30 days of the last dose of the study drugs for a follow up evaluation. Any assessments listed for the final visit should be performed at that time.

In addition, any of the following conditions require withdrawal of the subject from study treatment:

- Disease progression defined by irRECIST criteria
- Lost to follow up or non-compliance with the protocol schedule
- An AE or concurrent illness that in the opinion of the investigator or sponsor warrants the subject's withdrawal from treatment.
- Necessary treatment with other investigational drug or other anticancer medications prohibited by protocol
- Participation in another clinical study using anti-cancer agents
- Request by regulatory agencies for termination of treatment of an individual subject or all subjects under this protocol
- Sexually active subjects who refuse to use medically accepted barrier methods of contraception during the course of the study and for 4 months following discontinuation of study treatment
- Women who are pregnant or are breast feeding
- If the patient withdraws consent for continued participation, he/she will be removed from study.

The reason for study treatment discontinuation will be documented. For subjects who discontinue or are withdrawn from study treatment, every effort must be made to undertake protocol specified follow up procedures and end of treatment assessments, if possible unless consent to participate in the study is also withdrawn.

If a subject is discontinued from study treatment because of an AE considered to be related to study treatment and the event is ongoing 90 days after the last dose of study treatment, the event must be followed until resolution or determination by the investigator that the event has become stable or irreversible.

If a subject withdraws consent to participate in the study the reason for withdrawal will be documented, no further study procedures or assessments will be performed, and no further study data will be collected for this subject other than the determination of survival status from public records such as governmental vital statistics or obituaries.

6.6.2 Data Collection and Follow-up for Withdrawn Subjects

Patients will do off-study visit as long as all toxicity is resolved. The reason for study removal and date the patient was removed must be documented.

7. REGISTRATION PROCEDURES

7.1. CUMC Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures, along with applicable institutional policies and federal regulations.

Only Investigators/Research personnel properly trained and delegated to consent subjects for this protocol will participate in the consenting process. Furthermore, properly delegated/trained Physician Investigators (e.g., MD, MD/PhD) are required to sign/verify a protocol specific Eligibility Checklist for each subject enrolled on the study, in addition to providing the relevant source documentation confirmation subject eligibility.

All participants must be centrally registered through the Central Registration Office within Herbert Irving Comprehensive Cancer Center at CUMC prior to initiation of study treatment.

Registration hours are available Monday through Friday from 9:00am – 5:00pm EST (excluding holidays and weekends). Same day patient registrations (and after hour registrations) will be accommodated on a case by case basis provided that the study team has expressed all time sensitive registration concerns/cases in a timely manner to the Central Registration Office.

CPDM Central Registration Procedures:
Within 48 hours of obtaining consent (excluding holidays and weekends), a completed/signed IRB approved informed consent HIPAA form, and demographics forms must be submitted to the CPDM Central Registration Office via an email to CPDMRegistration@cumc.columbia.edu or fax to 212.305.5292, with the subject line "AAAR1581 Pending Subject Registration Request (PHI)". Upon receipt, applicable subject information as well as a "pending eligibility" status will be entered into HICCC's institutional database. This status will remain until further source documentation is made available to confirm overall patient eligibility. Required materials for all pending registration submissions are as follows:

- Completed/signed IRB approved/stamped Informed Consent Forms, including additional study ICFs for tissue.
- The completed/signed IRB approved HIPAA Authorization form
- Completed/signed CPDM ICF checklist
- Completed/signed HICCC personal census form
- Completed/signed CPDM Demographics Note to File

In order to confirm eligibility status, Investigators/designees (e.g., study specific Clinical Research Coordinator/Research Nurse, etc.) must submit the following documentation to the Central Registration Office via email or fax:

- The completed/signed study specific Eligibility Checklist (signed by an Physician level Investigator)

- Copies of source documentation necessary for each item to be verified on the CPDM specific Eligibility Checklist, including but not limited to:

    - Copy of required laboratory test and procedure reports (e.g., complete blood count, complete metabolic panel, cholesterol and triglycerides pregnancy test when applicable, MRI reports, CT/bone scans, etc.)

    - Copy of pathology and surgical reports

    - List of all prior malignancy-directed treatments

    - Copy of clinic note(s) or other appropriate medical records capturing the consent process information, along with providing source documentation of any other items needed for screening/eligibility that are not captured in other source document forms (e.g., positive investigator statements of unique eligibility items not captured via other direct source documentation, concomitant medication lists, etc.).

    - Protocol deviation/waiver approvals (if applicable)

    - **Please note**: subject line of email or fax should include the following: "Complete Subject Registration Request (PHI)".

Upon receipt of the above mentioned documentation, participant eligibility information will be verified by a qualified Central Registration Registrar. If any questions arise during the review process, queries in the form of emails will be addressed to the applicable study team personnel for clarification prior to enrollment. All applicable finalized registration/eligibility information will then be entered into HICCC's institutional CTMS database by the Central Registration Registrar. Upon completion, an official subject registration notification email will be sent to the PI/research team which will include eligibility/enrollment status, as well as subject ID information. Protocol therapy may not be initiated prior to receipt of this notification from the Central Registration Office.

All screen fail/ineligible subjects, as well as subject's who withdraw consent prior to enrollment/initiation of protocol therapy must be submitted to the Central Registration office in a manner analogous to the procedures noted above. Applicable source documentation will be required within the corresponding submissions.

7.2. Informed Consent Procedures

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal

Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

8. TREATMENT PLAN

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks for pembrolizumab and epacadostat are described in Section 8. Appropriate dose modifications for pembrolizumab and epacadostat are described in Section 9. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

8.1. Pembrolizumab Administration

Pembrolizumab is approved by the US Food and Drug Administration for the treatment of metastatic melanoma, non-small cell lung cancer, head and neck cancer, and unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options. Subjects will receive pembrolizumab 200 mg (flat dose) IV every 3 weeks on day 1 of a 21 day cycle.

Study treatment should be administered after all procedures/ assessments have been completed as detailed in the schedule of assessments (Section 12 & 13). All study treatments will be administered on an outpatient basis. Pembrolizumab will be administered as a 30 minute IV infusion. At the end of the infusion, the line should be flushed with a sufficient quantity of normal saline.

8.1.1. Management of Pembrolizumab Infusion Reactions

Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

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

Infusion Reaction Treatment Guidelines

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

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
	Subject is permanently discontinued from further trial treatment administration.	
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

8.2. Epacadostat Administration

Epacadostat will be dosed at 100 mg PO BID daily. Doses should be taken twice daily, in the morning and evening, approximately 12 hours apart, without regard to food. If a dose is late but within 4 hours of its scheduled administration time it should be taken; if more than 4 hours have passed, the dose should be omitted and the patient should continue treatment with the next scheduled dose. If vomiting occurs while taking epacadostat, no redosing is allowed before the next rescheduled dose.

For epacadostat, patients will not require any premedications, however supportive medications to control symptoms such as nausea, emesis, diarrhea, and pain will be provided for symptom control (Section 9.2 for management of immune related adverse effects).

Doses will be self-administered, except on Cycle 2 Day 1, when the morning dose will be given at the study site clinic. Subjects will be required to keep a pill diary (Appendix D). Each cycle of treatment will last 21 days.

8.3. General Concomitant Medication and Supportive Care Guidelines

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for 1 of these or other medications or vaccinations specifically prohibited during the study, discontinuation from study therapy may be required.

8.3.1. Restricted Medications and Measures

- Systemic steroids may be used at doses of prednisone ≤ 10 mg/day, or equivalent.

- Use of coumarin-based anticoagulants (eg, Coumadin) is discouraged. Low-dose Coumadin® (1 mg) is acceptable; however, doses that increase the INR are discouraged and will require dose modification. If an alternative to coumarin-based anticoagulants cannot be used, dose modifications of the Coumadin® may be needed. Based on the observed magnitude of epacadostat/warfarin PK interaction and PK/PD modeling results, for an epacadostat dose of 300 mg BID, the dose of warfarin should be reduced by approximately one-third after initiation of epacadostat administration based on approximately 30% to 40% reduction in S- and R-warfarin oral clearance values. Close

INR monitoring is recommended for subjects on a stable dose of warfarin who are starting treatment with epacadostat. Based on PK/PD modeling, recommendations for warfarin dose modifications for subjects receiving other epacadostat doses are summarized in Table below based on the INR prior to starting epacadostat.

Warfarin Dose Adjustment Recommendation when Initiating Concurrent Epacadostat Treatment

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

- Use of the anticonvulsant carbamazepine (a UGT1A9 inducer) is discouraged. Because there is a potential interaction that could result in lower epacadostat exposures, an alternative to carbamazepine should be used, if possible.

8.3.2. Prohibited Medications and Measures

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

- Any investigational medication other than the study drugs.
- Any anticancer medications, including chemotherapy or biologic therapy other than the study medications.
- Any immunological-based treatment for any reason.
    - Note: Inhaled or topical steroids are allowed, and systemic steroids at doses ≤ 10 mg/day prednisone or equivalents are allowed, and immune suppressants are allowed for treatment for immune toxicities.
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed after consultation with the principal investigator.
- Live Administration of live attenuated vaccines within 30 days before the first dose of study treatment and while participating in the study is prohibited. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.
- Any melatonin supplements.
- Any MAOI or drug associated with significant MAO inhibitory activity agents is prohibited from 21 days before Day 1 through 2 weeks after the final dose of epacadostat has been taken (see Appendix C).

- Any UGT1A9 inhibitor, including acitretin, amitriptyline, androsterone, cyclosporine, dasatinib, diclofenac, diflunisal, efavirenz, erlotinib, estradiol (17-beta), flutamide, gefitinib, gemfibrozil, glycyrrhetinic acid glycyrrhizin, imatinib, imipramine, ketoconazole, linoleic acid supplements, mefenamic acid, mycophenolic acid, niflumic acid, nilotinib, phenobarbital, phenylbutazone, phenytoin, probenecid propofol*, quinidine, ritonavir, sorafenib, sulfinpyrazone, valproic acid, and verapamil.
    - *Note – Propofol, when used for short-term sedation during surgical/biopsy procedures, is allowed after consultation with the principal investigator. The epacadostat dose may be taken on the morning of the procedure, and the evening dose held following the procedure. Epacadostat may be resumed the next day.

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

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

8.4. Treatment Compliance

Treatment compliance with all study-related medications should be emphasized to the subject by the site personnel. Subjects will bring all bottles of unopened, empty, and unused study drug with them to each study visit. The appropriate study personnel will maintain records of study drug receipt and dispensing. Any discrepancy regarding the dose administered and the reason for the discrepancy will be recorded in the electronic case report form (eCRF). At each clinic visit, patients will be questioned about their compliance with study drug administration, and their dosing diary should be reviewed. Bottles of study drug, including all bottles of unopened, partially opened, or empty bottles cannot be destroyed or returned to the depot until a monitor reviews and verifies all tablet counts for compliance. Compliance with pembrolizumab will also be documented in the medical record and monitored by the principal investigator of its designee.

8.5. Randomization and Blinding

Not applicable.

8.6. Duration of Treatment

The subject will continue to receive study treatment as long as the subject is receiving benefit from treatment and has not met any criteria for study withdrawal (Section 6.6). If the subject discontinues study treatment, the treatment phase will end and the subject will enter the follow-up phase (Section 12).

8.7. 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 an approach may extend beyond the typical time course of responses seen with cytotoxic agents and can manifest as a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

If radiologic imaging shows progressive disease (PD), tumor assessment should be repeated ≥ 4 weeks later to confirm PD, with the option of continuing treatment for clinically stable subjects while awaiting radiologic confirmation of progression. Clinically stable may be defined by the following criteria:

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

In determining whether the tumor burden has increased or decreased, investigators should consider all target lesions as well as non-target lesions. Subjects who are deemed clinically unstable are not required to have repeat imaging for confirmation. If radiologic progression is confirmed, then the subject will be discontinued from study treatment as specified in the Protocol, and the first radiographic evidence of PD should be the date of progression. If radiologic progression is not confirmed, then the subject should resume/continue study treatment and have their next scan according to the Protocol-specified schedule.

9. DOSE DELAYS/ MODIFICATIONS

9.1. Criteria and Procedures for Dose Modifications and Interruption

In some circumstances, it may be necessary to temporarily interrupt study treatments as a result of AEs that may have an unclear relationship to the study drug(s). If an interruption is necessary both study treatments should be interrupted.

Treatment with both study drugs should be withheld for drug-related Grade 4 hematologic toxicities, non-hematological toxicity ≥ Grade 3 (including laboratory abnormalities) or selected ≥ grade 2 immune-related toxicities (see section 9.2), and severe or life-threatening AEs.

Pembrolizumab must be permanently discontinued for Stevens Johnson Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN)

Table 1 summarizes the dose administration guidance for pembrolizumab and epacadostat that should be implemented with the indicated related AEs. Additional information related to dose changes for epacadostat and pembrolizumab for specific AEs can be found in Section 9.2.

Table 1: Dose Modification Guidelines for Drug-Related Adverse Events

Toxicity	Grade	Hold Treatment (Y/N)	Timing of Treatment Restart	Dose Schedule for Treatment Restart		Discontinue Subject
				Epacadostat	Pembrolizumab	
Hematologic Toxicity	1, 2, 3	No	N/A	N/A	N/A	N/A
	4	Yes	Toxicity resolves to ≤ Grade 1 or baseline	Reduce dose to 50 mg PO BID. If 50 mg PO BID is not tolerated, then epacadostat should be discontinued.	Restart at same dose for the following events: Grade 4 neutropenia lasting ≤ 7 days, Grade 4 lymphopenia or leukopenia. For all other Grade 4 Hematologic toxicities treatment with 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.
Non-Hematologic Toxicity Note: Exception to be treated similar to Grade 1 toxicity: - Grade 2 alopecia - Grade 2 fatigue - Grade 3 rash in the absence of desquamation, without mucosal involvement, not requiring systemic steroids, and that resolves to Grade 1 within 14 days **** See section 9.2 for immune-related AE's***	1	No	N/A	N/A	N/A	N/A
	2	Consider holding for persistent symptoms	Toxicity resolves to ≤ Grade 1 or baseline	Restart at same dose for non-immune related AEs ****See section 9.2 for management of immune-related AE's that may require dose reductions.*** If dose reduction is required: Reduce dose to 50 mg PO BID. If 50 mg PO BID is not tolerated, then epacadostat should be discontinued.	Restart at same dose ****See section 9.2 for management of immune-related AE's that may require dose reductions.***	Toxicity does not resolve within 6 weeks of last infusion. Permanent discontinuation should be considered for any severe or life-threatening event.
	3	Yes	Toxicity resolves to ≤ Grade 1 or baseline	Reduce dose to 50 mg PO BID. If 50 mg PO BID is not tolerated, then epacadostat should be discontinued.	Restart at same dose	Toxicity does not resolve within 6 weeks of last infusion. Permanent discontinuation should be considered for any severe of life-threatening event.
	4	Yes	Discontinue treatment	Treatment with epacadostat may not be restarted	Treatment with pembrolizumab may not be restarted	Toxicity does not resolve within 6 weeks of last infusion. Permanent discontinuation

						should be considered for any severe of 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.

9.2. Procedures for Subjects Exhibiting Immune-Related Adverse Events

This section is meant to apply to suspected immune-related adverse effects (irAEs) from epacadostat, pembrolizumab, or the combination. Immune-related AEs may be defined as an AE of unknown etiology, associated with drug exposure and consistent with an immune phenomenon. 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.

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.

9.2.1. Procedures and Guidelines for Pneumonitis

Subjects with symptomatic pneumonitis should immediately stop receiving pembrolizumab and epacadostat 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 2.

Table 2. Recommended Approach to Handling Noninfectious Pneumonitis.

	Withhold/ Discontinue Pembrolizumab and Epacadostat	**Guidance for Restarting Study Treatment**	**Supportive Care**
Grade 1	No action.	N/A.	Intervention not indicated.
Grade 2	Withhold pembrolizumab and epacadostat.	**First episode of pneumonitis:** • If improves to near baseline: o Decrease the dose of epacadostat to 50 mg BID, and for pembrolizumab restart at same dose and schedule for subsequent cycles. • If not improved after 2 weeks or worsening permanently discontinue pembrolizumab. **Second episode of pneumonitis:** • Permanently discontinue pembrolizumab and epacadostat if upon rechallenge subject	Systemic corticosteroids are indicated. Taper if necessary.

		develops pneumonitis ≥ Grade 2.	
Grade 3 and 4	Discontinue pembrolizumab and epacadostat.	Not applicable. Any exceptions require PI approval.	Systemic corticosteroids are indicated. The use of infliximab may be indicated as appropriate.

9.2.2. Procedures and Guidelines 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 3.

Table 3. Recommended Approach to Handling Enterocolitis.

	Withhold/ Discontinue Pembrolizumab and Epacadostat	**Guidance for Restarting Study Treatment**	**Supportive Care**
Grade 1	No action.	N/A.	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 ≤ 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 ≤ Grade 1 or baseline in 4 weeks, epacadostat should be reduced as per Table 1, but pembrolizumab may be restarted at the same dose and schedule. If AE does not resolve within 6 weeks, study treatment with	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.

		both study drugs should be discontinued.	
Grade 3 and 4	Discontinue pembrolizumab and epacadostat.	Not applicable. Any exceptions require PI 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.

9.2.3. Procedures and Guidelines for Hepatitis

Liver function 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 increased until resolution. Recommendations for management of hepatitis are shown in Table 4.

Table 4. Recommended Approach to Handling Hepatitis.

	Withhold/ Discontinue Pembrolizumab and Epacadostat	**Guidance for Restarting Study Treatment**	**Supportive Care**
Grade 1	No action.	N/A.	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 ≤ Grade 1 or baseline within 4 weeks, epacadostat should be reduced as per Table 1, but pembrolizumab may be restarted at the same dose and schedule.	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

		If AE does not resolve within 6 weeks, study treatment with both study drugs should be discontinued.	taper should be started and continued over at least 1 month.
Grade 3 and 4	Discontinue pembrolizumab and epacadostat.	Not applicable. Any exceptions require PI 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 $\leq$ Grade 1, corticosteroid taper should be started and continued over at least 1 month.

9.2.4. 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 5.

Table 5. Recommended Approach to Handling Dermatitis.

	Withhold/ Discontinue Pembrolizumab and Epacadostat	**Guidance for Restarting Study Treatment**	**Supportive Care**
Grade 1	No action.	N/A.	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	N/A.	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 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 necrosis, or rash complicated by full thickness dermal ulceration or by necrotic, bullous, or hemorrhagic manifestations.	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. If rash is mild and Grade 3 only based on BSA, and resolves without oral steroids, treatment may be restarted at the previous dose. For an AE that does not resolve to ≤ Grade 1 or baseline within 4 weeks, epacadostat should be reduced as per Table 1, 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.	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.

9.2.5. 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 parenthesis. Recommendations for management of neuropathies are shown in Table 6.

Table 6. Recommended Approach to Handling Neuropathies.

	Withhold/ Discontinue Pembrolizumab and Epacadostat	**Guidance for Restarting Study Treatment**	**Supportive Care**
Grade 1	No action.	N/A.	Provide symptomatic treatment.
Grade 2	May withhold pembrolizumab and epacadostat.	May return to treatment if improves to Grade 1 or baseline. 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 ≤ Grade 1 or baseline within 4	Consider systemic corticosteroids in addition to appropriate symptomatic treatment.

		weeks, epacadostat should be reduced as per Table 1, 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.	
Grade 3 and 4	Discontinue pembrolizumab and epacadostat.	Not applicable. Any exceptions require PI 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.

9.2.6. 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 present with fatigue, headache, mental status changes, abdominal pain, unusual bowel habits, and hypotension or with nonspecific symptoms which 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 7.

Table 7. Recommended Approach to Handling Endocrinopathies.

	Withhold/ Discontinue Pembrolizumab and Epacadostat	**Guidance for Restarting Study Treatment**	**Supportive Care**
Grade 1	No action.	N/A.	Provide symptomatic treatment.
Grade 2	May withhold pembrolizumab and epacadostat.	May return to treatment if improves to Grade 1 or baseline. If AE resolves within 4 weeks ≤ Grade 1 or baseline, subject may restart at the same dose and	Initiate systemic corticosteroids treatment at a dose of 1 to 2 mg/kg per day of prednisone or equivalent, and initiate

		schedule for both pembrolizumab and epacadostat. For an AE that does not resolve ≤ Grade 1 or baseline within 4 weeks, epacadostat should be reduced as per Table 1, 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.	appropriate hormone replacement therapy.
Grade 3	Withhold or discontinue pembrolizumab and epacadostat.	May return to treatment if improves to Grade 1 or baseline. If AE resolves ≤ 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 ≤ Grade 1 or baseline within 4 weeks, epacadostat should be reduced as per Table 1, 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.	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 PI 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.

9.2.7. 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.

9.3. Procedures for Subjects Exhibiting Serotonin Syndrome

There is a theoretical chance 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, including tremor, hyperreflexia, spontaneous, ocular, or inducible clonus, together with agitation, fever, diaphoresis, or muscle rigidity:

- Immediately interrupt epacadostat administration. *Administration of pembrolizumab may continue.*
- Immediately interrupt any SSRI or SNRI administration.
- Provide appropriate medical management of the subject until all signs/symptoms are resolved (eg, IV fluids and/or sympathomimetic amines for hypotension, benzodiazepines for agitation, administration of 5-hydroxytryptamine antagonists such as cyproheptadine).
- If subject chooses to remain in the study, restart treatment with epacadostat after the SSRI or SNRI has been discontinued, no sooner than 5 half-lives have elapsed for the specific SSRI or SNRI in question and after resolution of signs/symptoms of SS. The SSRI or SNRI treatment MAY NOT be restarted.
- If subject chooses to withdraw from the study, or must restart treatment with SSRI or SNRI, the subject should be scheduled for a follow-up visit. Treatment with SSRI or SNRI may be initiated 2 weeks after resolution of signs and symptoms of SS.

10. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

10.1. Adverse events

See sections 11.1.7 and 11.2.7 for a list of adverse events related to pembrolizumab and epacadostat, respectively.

10.2. Definitions

Adverse Event:
An adverse event (AE) is any untoward or unfavorable medical occurrence in a human subject, including abnormal sign, symptom or disease, temporally associated with the subject's participation in research, Please note: laboratory, vital signs or ECG abnormalities are to be recorded as Adverse Events only if they are medically relevant (clinically significant): symptomatic, requiring corrective treatment, leading to treatment discontinuation and/or fulfilling a seriousness criterion..

Therefore, abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event:

Adverse events are classified as serious or non-serious. A serious adverse event is any AE that is:

- fatal
- life-threatening
- requires inpatient hospitalization/prolongation of existing hospitalation, unless:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (procedures such as central line placements, paracentesis, pain control)
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of an SAE given above/below and not resulting in hospital administrations
    - social reasons and respite care in the absence of any deterioration in the patient's general condition
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious events should be regarded as non-serious adverse events.

Unanticipated Problem:

An unanticipated problem is any incident, experience or outcome involving risks to subjects or others in any human subjects research that meets all of the following criteria:

- Unexpected (in terms of nature, severity or frequency) given (a) the research procedures that are described in the IRB-approval protocol and informed consent document, and (b) the characteristics of the subject population being studied;

- Related or possibly related to participation in such research (e.g., there is a reasonable possibility that the incident, experience or outcome may have been caused by the procedures involved in such research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic or social harm) than was previously known or recognized.

Adverse Event Reporting Period
The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures (e.g., after the first dose of study treatment) to the end of the study treatment (e.g., last dose of study treatment) and/or follow-up. For this study, the study treatment follow-up is defined as 90 days following the last administration of study treatment, **or** 90 days **following the decision to remove the subject from study treatment, whichever is earliest.**

Baseline/Preexisting Condition
A baseline/preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or if the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

Abnormal Laboratory Values
A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management (e.g., change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.).

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.
Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should **not** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

10.3. Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

10.4. Reporting of Serious Adverse Events

10.4.1 IRB Notification by Sponsor-Investigator

Reports of all events (including follow-up information) that meet the definition of an unanticipated problem posing risk to subjects or others must be submitted to the IRB within one week (5 business days) following the occurrence of the unanticipated problem or the principal investigator's acquiring knowledge of the unanticipated problem in accordance with IRB policy. Additionally, the sponsor-investigator will submit a summary of all Unanticipated problems that occurred since the beginning of the study at the time of continuing review. Copies of each report and documentation of IRB notification and receipt will be kept in the Regulatory binder.

10.4.2 FDA Notification by Sponsor-Investigator

The Columbia University Medical Center Sponsor-Investigator, as holder of the IND, will be responsible for all communication with the FDA. Columbia University Medical Center Principal Investigator will report to the FDA, regardless of the site of occurrence, any adverse event that is serious, unexpected and there is evidence to suggest a causal relationship between the drug and the adverse event. These must be reported to the FDA and any affiliate sites as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting. The Sponsor-Investigator will also submit an IND annual report to the

FDA in accordance with 21.CFR 312.33.

The Columbia University Medical Center Sponsor Investigator must report to the FDA and any affiliate site investigators as follows:

- Any unexpected fatal or life-threatening event must be reported as soon as possible, but no later than 7 calendar days after the sponsor investigator initial receipt of the information
- Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND, and whether or not conducted by the sponsor-investigator, that suggest a significant risk in humans exposed to the drug must be reported as soon as possible but no later than 15 calendar days after the sponsor-investigator determines that the information qualifies for reporting
- Any findings from animal or in vitro testing whether or not conducted under an IND, and whether or not conducted by the sponsor-investigator, that suggest a significant risk in humans exposed to the drug must be reported as soon as possible but no later than 15 calendar days after the sponsor-investigator determines that the information qualifies for reporting
- Any clinically important increase in the rate of a serious suspected adverse reactions over that listed in the protocol or Investigator Brochure
- Expected SAEs and AEs will be included in the IND Annual Reports.

Follow-up information to a safety report should be submitted as soon as the relevant information is available. However, if the results of a sponsor's investigation show that an adverse drug experience not initially determined to be reportable are so reportable, the sponsor investigator must report such experience as soon as possible, but no later than 15 calendar days after the determination is made.

All other serious unexpected experiences associated with the use of the study treatment will be reported to FDA as soon as possible but in no event later than 15 calendar days after initial receipt of the information.

10.4.3 DSMC Reporting by the Sponsor Investigator

Serious adverse events not constituting unanticipated problems are to be reported to the HICCC DSMC. Reporting should occur within 24 hours of knowledge of the SAE occurring at our institution or affiliate sites. CUMC will notify the HICCC DSMC within 24 hours of knowledge of the SAE once informed by the affiliate site.

Participating investigators must report each serious adverse event to the Columbia University Medical Center Overall Principal Investigator within 24 hours of learning of the occurrence using the SAE Report Form. In the event that the participating investigator does not become aware of the serious adverse event **immediately** (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the adverse event. Report serious adverse events by telephone, email or facsimile to:

Richard D. Carvajal, MD
177 Fort Washington Avenue, MHB 6GN-435
New York, NY 10032

Telephone: 646-317-6354
Fax: 212-305-3035
Email address: CPDM_R1581@lists.cumc.columbia.edu

Within the following 24-48 hours, the participating investigator must provide follow-up information on the serious adverse event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

10.4.4 Reporting to Drug Manufacturer by Sponsor-Investigator (Incyte)

All Serious Adverse Events ("SAE"), including pregnancy and lactation exposure, required to be reported pursuant to the Protocol shall be provided to Incyte and its representatives by Institution or Principal Investigator within **twenty-four (24) hours** of learning of the event as well as any additional reports agreed upon by Institution or Principal Investigator and Incyte.

SAE Reports will be sent to: Incyte PhVOpsIST@incyte.com.

By sending to this e-mail address, the Incyte Pharmacovigilance group will receive copies of the reports. This process will be tested and established before the first patient is enrolled in the Study. Notwithstanding anything to the contrary herein, Institution will have the primary responsibility of reporting adverse events ("AE") to regulatory authorities.

10.4.5 Reporting to Drug Manufacturer by Sponsor-Investigator (Merck)

For the time period beginning after the first dose of study treatment, any serious adverse event, or follow up to a serious adverse event, including death due to any cause that occurs to any participant must be reported within 24 hours to the Sponsor and within **2 working days** to Merck Global Safety if it causes the participant to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning after the first dose of study treatment through 90 days following cessation of treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause whether or not related to the Merck product, must be reported within 24 hours to the Sponsor and **within 2 working days** to Merck Global Safety.

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

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

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-661-6229

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 215-661-6229) at the time of submission to FDA.

10.4.6. Reporting Process

Adverse events may be submitted on FDA Form 3500A, the HICCC DSMC Serious Adverse Event Reporting Form, or in a narrative format. If supplied as in a narrative format, the minimum information to be supplied is noted above at the beginning of section 10.

At the time of IRB renewal or at the request of the manufacturer, the Sponsor- Investigator will submit a summary of all Serious Adverse Events that have occurred inclusive of all sites to manufacturer.

11. PHARMACEUTICAL INFORMATION

11.1. Pembrolizumab

11.1.1. Dispensing of Pembrolizumab

An initial bulk supply of pembrolizumab will be provided to investigative sites prior to enrollment of the first subject. Thereafter, the site will contact the sponsor for re-supply of pembrolizumab. The investigator or designee will calculate the number of pembrolizumab vials needed, pull the appropriate number of vials to prepare the infusion solution, and enter the vials used into the eCRF and drug accountability log. The Principal Investigator must keep accurate and up-to-date dispensation records. Any discrepancies between the amounts of Study drug dispensed and returned must also be explained in writing. All such records of drug accountability must be entered on the corresponding Subject CRF's.

11.1.2. Packaging and Formulation

Clinical Supplies will be provided by Merck as summarized in the table below

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

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

11.1.3. Storage

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.

11.1.4. Administration

Administer intravenously over 30 minutes. Do not co-administer other drugs through the same infusion line. See section 8.1 for details on pembrolizumab and administration and Section 8.1.1 for management of infusion reactions.

11.1.5. Disposal

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.

11.1.6. Drug interactions and Concomitant therapy

No formal pharmacokinetic drug interaction studies have been conducted with pembrolizumab.

11.1.7. Adverse Events

Common side effects (≥10% by frequency) seen with Pembrolizumab in patients with melanoma include the following:

Most Common Adverse Events in Subjects Treated with Pembrolizumab [33]

Adverse Event	N (Total = 2799)	(%)
Fatigue	1044	37.3%

Nausea	685	24.5%
Decreased appetite	630	22.5%
Diarrhea	625	22.3%
Cough	615	22.0%
Pruritus	562	20.1%
Arthralgia	504	18.0%
Rash	499	17.8%
Asthenia	362	12.9%
Pyrexia	357	12.8%

Adverse Events of Special Interest In Subjects Treated with Pembrolizumab [33]

Adverse Event	**N (Total = 2799)**	**(%)**
Hypothyroidism	237	8.5%
Hyperthyroidism	96	3.4%
Pneumonitis	94	3.4%
Infusion reactions	70	2.5%
Colitis	49	1.8%
Severe skin reactions	46	1.6%
Autoimmune hepatitis	19	0.7%
Adrenal insufficiency	22	0.8%
Hypophysitis	17	0.6%
Uveitis	14	0.5%
Myositis	11	0.4%
Pancreatitis	9	0.3%
Type 1 diabetes mellitus	6	0.2%
Guillain-Barre Syndrome	2	0.1%

Additional risks associated with pembrolizumab that have been identified are: Steven Johnson's Syndrome (SJS), myocarditis, and Toxic Epidermal Necrolysis (TEN)

11.2. Epacadostat

11.2.1. Dispensing of Epacadostat

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

11.2.2. Packaging and Formulation

The drug is available at 25 mg, 100 mg, and 300 mg tablets. The drug will be packaged in high-density polyethylene bottles. All bottles will be labeled with a statement such as: "Caution: New Drug—Limited by Federal Law to Investigational Use."

11.2.3. Storage

Epacadostat should be stored at ambient conditions (15-30° C). The study drug provided in accordance with this Protocol will be kept in a secure place, and will only be supplied to subjects participating in this study.

11.2.4. Administration

Epacadostat should be taken twice daily, in the morning and evening, approximately 12 hours apart, without regard to food. If a dose is late but within 4 hours of its scheduled administration time it should be taken; if more than 4 hours have passed, the dose should be omitted and the patient should continue treatment with the next scheduled dose.

11.2.5. Disposal

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

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

11.2.6. Drug interactions and Concomitant therapy

See Section 8.3 for details of restricted concomitant therapy.

11.2.7. Adverse Events

Common side effects (≥10% by frequency) seen with epacadostat monotherapy in patients enrolled on a Phase 1 clinical trial:

Adverse Reactions in ≥10% of Patients in Phase 1 trial of Epacadostat.

Adverse Reaction	All grades (%)
General	
Fatigue	69.2%
Pyrexia	15.4
Gastrointestinal	

Nausea	65.4
Diarrhea	26.9
Constipation	36.5
Abdominal Pain	28.8
Respiratory	
Dyspnea	25
Cough	21.2
Skin	
Rash	17.6
Metabolism	
Decreased appetite	53.8
Musculoskeletal	
Back pain	25
Nervous System	
Dizziness	11.5

12. STUDY EVALUATIONS

12.1. Screening Phase

The screening phase will be up to 28 days. Screening is the interval between the signing of the informed consent form (ICF) and the day the subject receives the first dose of treatment in the study (Cycle 1 Day 1). Informed consent must be obtained before performing any study-specific procedures not considered standard of care. Assessments that are required to demonstrate eligibility may be performed over the course of 1 or more days during this phase.

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

See Section 13 (table 10-11) for detailed list of screening procedures.

12.2. Treatment Phase

The treatment period will continue every 21 days and may continue as long as subjects are receiving benefit from treatment and have not met any criteria for study withdrawal.

See Section 13 (Table 10 and Table 11) for detailed list and schedule of procedures while on

treatment.

12.2.1. Clinic Visits

During Cycle 1, patients will be seen weekly for vitals, physical exam, assessment of adverse effects, and appropriate laboratory tests and procedures (Section 13, Table 10 and table 11). Starting Cycle 2 and onward, patients will be seen on Day 1 of each cycle for vitals, physical exam, assessment of adverse effects, and appropriate laboratory tests and procedures. Patients may be seen for additional unscheduled visits as needed at the discretion of the investigator.

12.2.2. Assessment for Serotonin syndrome

Subjects will be assessed for the presence of any of the following symptoms (Table 8) of serotonin syndrome at the time points indicated in the study calendar.

Table 8: Symptoms of Serotonin Syndrome

Tremor and hyper-reflexia
Spontaneous clonus
Muscle rigidity, temperature > 38 C, and either ocular clonus or inducible clonus
Ocular clonus and either agitation or diaphoresis
Inducible clonus and either agitation or diaphoresis

12.2.3. General laboratory assessment.

See Table 11 and 12 for detailed laboratory tests and timing of these tests.

12.2.4. Schedule of Disease monitoring.

A CT scan of the chest, abdomen, and pelvis with contrast will be obtained to evaluate disease status. A scan will be obtained at baseline (within 28 days of first study drug dose), then every 6 weeks for the first 24 weeks (imaging of the area with known disease involvement only (ex: CT chest only or CT abdomen/ pelvis only) is allowed for week 6 and week 18 tumor assessments at the investigator's discretion)). After week 24, a CT chest, abdomen, pelvis with contrast will be performed every 12 weeks until disease progression, withdrawal from study, or ongoing disease control at 2 years (defined as at least stable disease at this point). For patients who achieve ongoing disease control at 2 years, treatment will be stopped and subjects will be observed with a CT scan every 12 weeks. If the patient develops disease progression during this observation time, they will have the option of restarting study treatment at that time.

Table 9: Schedule of Disease Monitoring.

Baseline scan	Baseline scan within 4 weeks prior to first treatment
Weeks 1 – 24	Every 6 weeks +/- 1 week (at weeks 6, 12, 18, 24)
Weeks 25 – until disease progression	Every 12 weeks +/- 1 week (at weeks 36, 48, 60, 72, 84, 96, 108)

2 years	If subjects achieve ongoing disease control at 2 years, patients will be taken off study treatment and observed with imaging every 12 weeks +/- 2 week. If the patient develops disease progression, the option of re-initiating study therapy may be considered.

12.2.5. Collection of Tumor Biopsies and Blood for Correlative Studies

All enrolled subjects must undergo pre- and on-treatment research tumor biopsies. Subjects in whom biopsy is technically not feasible or in whom would result in unacceptable risk, in the opinion of the investigator, may be exempted from the biopsy requirement with discussion with the principal investigator. Use of outside archived tumor tissue for a baseline biopsy is not permitted. Biopsies will be collected at baseline and between C2D1 and C3D1 of therapy for correlative studies. An optional research biopsy at the time of progression will also be discussed with these patients, however, is not mandatory.

12.2.6. Adverse Events Monitoring

Adverse events will be monitored from the time the subject signs the ICF. Subjects will be instructed to report all AEs during the study and will be assessed for the occurrence of AEs throughout the study. All AEs (serious and nonserious) must be recorded on the source documents and eCRFs regardless of the assumption of a causal relationship with the study drug. The definition, reporting, and recording requirements for AEs are described in Section 10.

All AEs of unknown etiology associated with pembrolizumab and epacadostat exposure should be evaluated to determine if it is possibly an irAE.

12.3. End of Treatment

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

12.4. Follow-up Phase

12.4.1. Safety Follow-up

The safety follow-up phase is the interval between the last dose of study treatment and the scheduled safety follow-up visits, which should occur on days 30 (+/- 7 days) after the EOT visit. Adverse events and SAEs must be reported up until at least 90 days after the last dose of study drug, or until study drug-related toxicities resolve, return to baseline, or are deemed irreversible,

whichever is longer. If a subject initiates a new anti-cancer therapy within 90 days after the last dose of study treatment, the next scheduled safety follow-up visit must occur before the first dose the new therapy. Once new anti-cancer therapy has been initiated, the subject will move into the survival follow-up phase.

12.4.2. Follow-up (patients taken off treatment for reasons other than POD)

Subjects who discontinue study treatment for a reason other than disease progression (including patients who achieve stable disease control at 2 years) will move into the follow-up phase and will be assessed every 12 weeks by radiologic imaging to monitor disease status.

For patients who achieved stable disease at 2 years, re-treatment on study may be allowed at the time of disease recurrence or progression with permission of the study PI.

Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, and end of the study.

12.4.3. Survival Follow-up

Once a subject has confirmed disease progression or starts a new anticancer therapy, the subject moves into the survival follow-up phase and should be contacted by telephone, email, or visit every 12 weeks (+/- 2 weeks) to assess survival status. Clinical notes for patients currently being treated at Columbia University Medical Center (or collaborating medical center) will also suffice as follow up. Overall survival will be followed until death, withdrawal of consent, or the end of the study, whichever occurs first.

12.5. Unscheduled Visits

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

13. STUDY CALENDAR

All study assessments will be performed as indicated in the schedules of assessments in Table 10 – Table 13 below.

Table 10. Schedule of Assessments for Screening Through Treatment Phase

	Screening	Cycle 1			Cycle 2	All subsequent cycles [2, 16]
Procedure	Day –28 to –1 [1]	C1D1	C1D8 ± 3d	C1D15 ± 3d	C2D1 ± 3d	Day 1 ± 3d
Informed Consent	X					
Inclusion/ Exclusion Criteria	X					
Past Medical and Cancer History	X					
GIST diagnosis confirmation by site pathologist [3]	X					
Concomitant medication review [4]	X	X	X	X	X	X
Physical examination, vital signs[5]	X	X	X	X	X	X
Height	X					
Weight	X	X			X	X
ECOG Performance Status	X	X			X	X
Laboratory assessments [6]	X	X	X	X	X	X
EKG	X					
O2 saturation [7]	X	X	X	X	X	X
Serum pregnancy test[8]	X					
Assess for Serotonin Syndrome[9]			X	X	X	X
Adverse events		X	X	X	X	X
Study drug compliance (Pill diary)					X	X
CT chest, abdomen, pelvis [10]	X				X [10]	
Fresh tumor biopsy	X [11]				X [12]	
Blood for correlative study analysis		X [13]			X [13]	X [13]
Blood for PD analysis (fasting)		X [14]			X [14]	
Administer pembrolizumab		X			X	X
Administer/ dispense epacadostat [15]		X [15]			X [15]	X

1. Protocol-specified screening procedures that are performed as part of standard of care and within 28 days of Day 1 of Cycle 1 may be used for screening purposes. Clinical laboratory studies must be performed within 28 days before Cycle 1 Day 1, and baseline CT scan must be performed within the 28-day period before Day 1 of Cycle 1.
2. If the study treatment is well tolerated, then the clinic visit, laboratory studies and other procedures indicated in the column (except CT chest/abdomen/pelvis – see footnote 10) will be performed every 3 weeks at the beginning of each subsequent cycle.
3. Initial diagnostic slides (if archived slides are available) will be requested and reviewed by site pathologist to confirm diagnosis of GIST for the patient to be considered for the study.
4. Concomitant medications will include non-prescribed medications and any complementary/herbal supplements.
5. A complete physical examination will be performed at screening and each subsequent

visit.

6. For complete list of laboratory assessments, see Table 11.
7. Resting O2 saturation should be assessed at each visit. Ambulatory O2 saturation (after mild to moderate exertion) should be checked as clinically indicated.
8. Only required in women of child-bearing potential.
9. See section 12.2.2 for assessment of serotonin syndrome.
10. CT chest, abdomen, and pelvis with contrast to assess tumor status will be performed at baseline (within 28 days prior to Cycle 1 Day 1 of treatment) and then every 6 weeks (+/- 1 week) during the first 24 weeks of study treatment. Imaging of the area with known disease involvement only (ex: CT chest only or CT abdomen/ pelvis only) is allowed for week 6 and week 18 tumor assessments at the investigator's discretion. After week 24, a CT chest, abdomen, pelvis with contrast will be performed every 12 weeks (+/- 1 week). In patients who are unable to get a CT scan with contrast due to renal function (or any other reason), a CT chest without contrast and MRI abdomen/ pelvis with and without contrast may be used instead.
11. A fresh tumor biopsy will be performed at baseline within screening period, prior to C1D1 of treatment. Archived FFPE slides are not acceptable. This biopsy is mandatory. However, subjects in whom biopsy is technically not feasible or in whom would result in unacceptable risk, in the opinion of the investigator, may be exempted from the biopsy requirement with discussion with the principal investigator.
12. On-treatment biopsy will be obtained anytime between C2D1 and C3D1 (prior to starting cycle 3). This biopsy is mandatory. However, subjects in whom biopsy is technically not feasible or in whom would result in unacceptable risk, in the opinion of the investigator, may be exempted from the biopsy requirement with discussion with the principal investigator.
13. Blood for ctDNA will be collected on day 1 ± 3d for cycles 1-3, and then day 1 ± 3d of every other cycle thereafter. In addition, blood for PBMC collection will be collected on cycle 1 day 1 and cycle 2 day 1 (± 3d). See section 14.1.2 for collection instructions.
14. A fasting blood sample for PD analysis will be collected on Cycle 1, Day 1 (pre-dose) and Cycle 2, Day 1 ± 3d (pre-dose and +2 hours (+/- 30 minutes)), and at the end of treatment. See section 14.1.3 for collection instructions.
15. One full cycle (21 days) supply of epacadostat will be dispensed at the beginning of each subsequent cycle. Cycle 2, Day 1 epacadostat dose will be administered in clinic (for PD blood sample studies).
16. For subjects who restart treatment after achieving disease control following 2 years of therapy, procedures will restart following the schedule for all subsequent cycles. CT chest/ abdomen/ pelvis with contrast will be performed every 12 weeks (+/- 1 week) in these patients.

Table 11. Laboratory Assessments for Screening Through Treatment Phase

	Screening	Cycle 1			Cycle 2	All subsequent cycles
Procedure	Day –28 to –1 [1]	C1D1	C1D8 ± 3d	C1D15 ± 3d	C2D1 ± 3d	Day 1 ± 3d
Chemistry [2]	X	X			X	X
CBC with differential [3]	X	X			X	X
Liver function tests [4]	X	X	X	X	X	X
TSH and Free T4 (FT4) and Total thriiodothyronine (T3)	X	X			X	X
INR and PTT [5]	X					
Serum pregnancy test [6]	X					
Urine or serum pregnancy test [6]		X			X	X
Serology for HBV and HCV [7]	X					
Blood for correlative studies [8]		X			X	X
Blood for PD analysis (fasting) [9]		X [9]			X [9]	

1. Baseline clinical laboratory studies must be performed within 28 days before Cycle 1 Day 1.
2. Chemistry testing includes: Serum sodium, potassium, chloride, carbon dioxide, blood urea nitrogen, creatinine, glucose, calcium, magnesium, phosphorus, lactate dehydrogenase
3. CBC testing includes: WBC count with differential, hemoglobin, hematocrit, platelet count
4. LFTs include: AST, ALT, total bilirubin, and alkaline phosphatase, albumin, protein.
5. INR and PTT and required only at screening, but may be followed if clinically indicated.
6. Only in women of child-bearing potential.
7. Serology for HBV and HCV includes: Hepatitis B surface antigen (HBsAg) and Hepatitis C virus Antibody (HCV Ab). If Hepatitis C antibody is positive, reflex to check hepatitis C quantitative RNA.
8. Blood for research correlative studies (non-fasting): Blood samples for ctDNA will be collected on day 1 ± 3d for cycles 1-3, and then day 1 ± 3d of every other cycle thereafter. Blood for PBMC collection will be collected on cycle 1 day 1 and cycle 2 day 1 (± 3d). See section 14.1.2 for collection instructions.
9. A fasting blood sample for PD analysis will be collected on Cycle 1, Day 1 (pre-dose) and Cycle 2, Day 1 ± 3d (pre-dose and +2 hours (+/- 30 minutes)), and at the end of treatment. See section 14.1.3 for collection instructions.

Table 12. Schedule of Assessments for End of Treatment (EOT) through Follow-up Phase

PROCEDURE	EOT[1]	Follow-up Phase		
		Safety Follow-up [1]		
	+ 7 days	30 days after EOT +/- 7 days	Follow-up (Every 12 weeks) +/- 14 days [2]	Survival Follow-up (Every 12 weeks) +/- 14 days
Concomitant medication review	X	X		
Comprehensive physical exam	X			
Targeted physical exam		X		
Assess for serotonin syndrome	X			
Vital signs and weight	X	X		
O2 saturation	X	X		
ECOG performance status	X	X		
AE assessment[1]	X	X[1]		
Laboratory assessments [3]	X	X		
Radiologic tumor assessments	X [4]		X [5]	
Fresh tissue collection	X [6]			
Blood for correlative studies	X [7]			
Blood for PD analysis (fasting)	X [8]			
Post-study anti-cancer therapy status			X	X
Survival follow-up			X	X

1. Subjects must be followed for AEs and SAEs for **90 days** after the last dose of study drug.
2. Subjects will be assessed by either a clinic visit or telephone contact every 12 weeks from the last dose of study treatment.
3. Safety laboratory assessments will be collected at EOT and at the each safety follow-up visit. See table 13 for detailed laboratory tests.
4. If a prior scan was obtained within 4 weeks before the date of discontinuation, then a scan at treatment discontinuation is not mandatory. In subjects who discontinue study therapy without confirmed disease progression, a radiological evaluation should be repeated at the time of treatment discontinuation (+/- 4 week window).
5. For subjects who discontinue treatment for reasons other than disease progression, every effort should be made to continue monitoring their disease status by radiographic imaging every 12 weeks until (1) start of new anticancer therapy, (2) documented disease progression, (3) death, or (4) the end of study, whichever occurs first.
6. An optional tumor biopsy sample for research purposes can be obtained at the time of disease progression.

7. See section 14.1.2 for instructions on blood collection for research correlative analysis.
8. See section 14.1.3 for instructions on blood collection for PD analysis.

Table 13. Laboratory Assessments for End of Treatment and Follow-up Phase

PROCEDURE	EOT	Follow-up Phase		
		Safety Follow-up		
	+ 7 days	30 days after EOT +/- 7 days	Follow-up (Every 12 weeks) +/- 14 days	Survival Follow-up (Every 12 weeks) +/- 14 days
Chemistry [1]	X	X		
CBC w/ differential [2]	X	X		
Liver function testing (LFT) [3]	X	X		
TSH and Free T4 (FT4) and Total thriiodothyronine (T3)	X			
Urine or serum pregnancy test [4]	X			
Blood for correlative studies [5]	X			
Blood for PD analysis (fasting) [6]	X			

1. Chemistry testing includes: Serum sodium, potassium, chloride, carbon dioxide, blood urea nitrogen, creatinine, glucose, calcium, magnesium, phosphorus, lactate dehydrogenase
2. CBC testing includes: WBC count with differential, hemoglobin, hematocrit, platelet count
3. LFTs include: AST, ALT, total bilirubin, alkaline phosphatase, albumin, protein.
4. For female subjects of childbearing potential only.
5. Blood (non-fasting) will be collected for research correlative analysis (for ctDNA and PBMC collection). See section 14.1.2 for collection instructions.
6. A fasting blood sample for PD analysis will be collected at the end of treatment. See section 14.1.3 for collection instructions.

14. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

14.1. Collection of samples for correlative studies

14.1.1. Tumor biopsy samples

Pre- and on-treatment tumor biopsies are mandatory. Subjects in whom biopsy is technically not feasible or in whom would result in unacceptable risk, in the opinion of the investigator, may be exempted from the biopsy requirement, with discussion with the principal investigator.

Timing of Biopsy Samples:

A fresh biopsy must be obtained at the following time-points:

- Prior to treatment (anytime during the screening period) (mandatory)
- On-treatment (between C2D1 and C3D1 treatment dose)) (mandatory)
- At the time of disease progression (optional)

Collection & Processing Instructions:

Collection and processing instructions are the same for all of the specified tumor biopsy time points.

A goal of at least 3 cores and up to 8 cores, if safe to obtain, will be obtained at each collection time point.

See laboratory manual for detailed processing and shipping instructions for all correlative study specimens.

Shipping Instructions:

Shipments will be sent to the Schwartz laboratory by batch shipments when possible.

Schwartz Laboratory
1130 Saint Nicholas Avenue
ICRC Room 207
New York, NY 10032

The analyzing laboratories should be notified by email (Study listserv email: CPDM_R1581@lists.cumc.columbia.edu) and Grazia Ambrosini (ga2391@cumc.columbia.edu)) the day the samples are sent. The email will contain the following information:

- Subject ID number
- Subject Initials
- Date of collection

- Time point (e.g. baseline, Cycle 2 Day 1, end of treatment, etc)
- Name of study center
- Shipment date
- Contents of shipment

All samples should be directed to the address listed above. Samples should be shipped via courier so that the package is tracked appropriately (specifically Federal Express or UPS). The samples should be shipped for morning delivery, Monday through Thursday for optimal processing.

Samples will be tracked through a Microsoft Excel tracker.

14.1.2. Peripheral blood samples

Blood samples will be used for correlative studies, including, but not limited to, peripheral blood lymphocyte subset and cytokine analysis. All peripheral blood samples are mandatory.

Blood for ctDNA analysis will be collected at the following time points:

- Day 1 ± 3d for cycles 1-3, Day 1 ± 3d of every other cycle thereafter
- End of study

Blood for PBMC isolation will be collected at the following time points:

- Day 1 Day 1, Cycle 1 Day 2 ± 3d
- End of study

Blood (non-fasting) will be collected for research purposes for PBMC isolation and ctDNA studies described below in section 14.2.

<u>See laboratory manual for detailed processing and shipping instructions for all correlative study specimens.</u>

14.1.3 Blood samples for Phamacodynamic (PD)/ IDO analysis

IDO Phamacodynamic (PD) analysis:

IDO inhibition will be assessed through analysis of tryptophan metabolites.

Patients should be fasting for each of these draws. Patients will withhold their morning dose of epacadostat on Cycle 2 Day 1. After the pre-dose sample is draw, subjects will take epacadostat and then receive their infusion of pembrolizumab. The timing of the sample for PD analysis below is relative to the timing of epacadostat administration.

A fasting blood sample will be obtained at:

- Cycle 1 Day 1 (Pre dose)
- Cycle 2 Day 1 ± 3d (Pre dose, + 2 hours (± 30 minutes))
- End of treatment

See laboratory manual for detailed processing and shipping instructions for all correlative study specimens.

14.2. Correlative Studies

Tissue and blood samples may be used for the following correlative studies. Additional studies may be included in the future.

14.2.1. IDO activity and expression

IDO Activity
Pre- and post-treatment samples will be analyzed for IDO activity by measurement of tryptophan and the tryptophan metabolite, kynurenine, using liquid chromatography with tandem mass spectrometry.

IDO Expression
IDO protein expression will be analyzed by IHC.

14.2.2. Tumor Infiltrating Lymphocytes

Lymphocyte subsets will be analyzed by IHC for CD3, CD4, CD8, and Foxp3 on FFPE sections using IHC with digital quantification.

14.2.3. PD-L1 expression

Baseline tumor PD-L1 will be assessed by IHC.

14.2.4. Whole exome sequencing

To further characterize the mutational landscape of GIST tumors, whole exome sequencing (WES) may be performed on baseline tumor tissue samples if sufficient funding is available. As WES is being performed for research purposes only, the results of WES testing will not be shared with the subject or their treating physician. Smaller targeted cancer panels may be performed; in particular, KIT mutation status will be analyzed if not already known.

14.2.5 Cell-free DNA

Cell-free DNA will be evaluated as a measure of tumor burden and response to therapy.

15. MEASUREMENT OF EFFECT

15.1. Antitumor Effect – Solid Tumors

Initial tumor imaging must be performed within 28 days before the first dose of study treatment. For the purposes of this study, patients should be re-evaluated for response every six weeks within the first 24 weeks, then every 12 weeks for the remainder of study duration (Section 7.2.6). The study will utilize RECIST v.1.1, with responses confirmed at ≥4 weeks, for determination of the primary endpoint of ORR. The immune related RECIST (irRECIST), which is adapted for defining PD to account for the unique tumor response seen with immunotherapies (section 15), will be applied for clinical assessment of tumor response and as a basis for treating subjects beyond initial radiographic progression.

15.2. Definitions

Evaluable for objective response: Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response: Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

15.3. Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

15.4. Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy/Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [JNCI 96:487-488, 2004; J Clin

Oncol 17, 3461-3467, 1999; J Clin Oncol 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [JNCI 92:1534-1535, 2000].

Cytology/Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

15.5. Response Criteria

NOTE: Clinical decision making can be made by irRECIST (that is, patients may be treated beyond progression) but the primary endpoint will be assessed by RECIST v. 1.1.

Assessment of Disease According to Immune Related RECIST for Solid Tumors

The immune related RECIST (irRECIST), which is adapted to account for the unique tumor response seen with immunotherapies, will be applied for response evaluation.[34]

The irRECST criteria considers index lesions identified at baseline together with new lesions that may occur after the start of treatment, and are incorporated into the calculated tumor burden. The appearance of new lesions alone does not constitute PD.

If imaging shows PD, tumor assessment should be repeated ≥4 weeks later to confirm PD with the option of continuing treatment for clinically stable subjects.

Confirmation of progression will be defined as a >10% increase in tumor burden on a subsequent scan (performed at ≥4 weeks) when compared to the initial progression scan.

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

15.5.1. Evaluation of Target Lesions by irRECIST

Tumor burden = Sum of diameter (target) + Sum of diameter (new)

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the tumor burden compared with baseline.

Progressive Disease (PD): At least a 20% increase in the tumor burden compared, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study), with confirmation of progression by a scan at least 4 weeks later (Note: With irRECIST, the appearance of new lesions alone is not considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

15.5.2. Evaluation by Choi Criteria

Evaluation of response by Choi Criteria, which is a validated response criteria for GIST using change in radiographic density, will be performed for secondary endpoint analysis.

"Size" refers to the change from the baseline of the sum of longest diameters of all target measurable lesions, as in RECIST criteria.

Complete Response (CR): Disappearance of all disease. No new lesions.

Partial Response (PR): A decrease in size of ≥ 10% OR a decrease in CT density (HU) ≥ 15%. No new lesions. No obvious progression of non-measurable disease.

Stable Disease (SD): Does not meet the criteria for CR, PR, or PD. No symptomatic deterioration attributed to tumor progression.

Progression of Disease (PD): An increase in uni-dimensional tumor size of ≥ 10% AND did not meet criteria for PR by CT density. Any new lesions, including new tumor nodules in a previous cystic tumor.

15.6. Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

For patients who have not progressed or died, their follow-up will be censored at the time of last clinical evaluation.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

15.7. Progression-Free Survival (PFS)

PFS is defined as the duration of time from enrollment to time of progression or death, whichever occurs first. For patients who have not progressed or died, their follow-up will be censored at the time of last clinical evaluation.

15.8. Response Review

Not applicable.

15.9. Unblinding Procedures

Not applicable.

15.10. Stopping Rules

The study may be discontinued if the study is terminated by the data and safety monitoring committee, the Food and Drug Administration (FDA), or other regulatory authorities.

Any unforeseen deaths or serious adverse events may, after a discussion between the principal investigator and investigators at other sites, prompt an interruption to study accrual pending a full investigation into the circumstances surrounding the event.

15.11. Other Response Parameters

Not applicable.

16. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 10 (Adverse Events: List and Reporting Requirements). The Data Safety Monitoring Plan is described in Section 16.

16.1. Data Collection

The Herbert Irving Comprehensive Cancer Center has an electronic clinical trials and data management system (CTMS) that will be used for data collection. Case report forms (CRFs) for the study will be built into the CTMS for data entry. The system has full auditing capabilities which is web-based and housed on a server in a fully HIPAA compliant server room with restricted access and video camera monitoring. All users must login with their own application username and password. Users off campus must first access the Virtual Private Network with their assigned campus username and password and then use their application credentials. Users are only able to see study information if they are indicated as study personnel in our electronic IRB system. Users are limited to access based on the role assigned in their corresponding protocol. Subject data is entered directly into the system, which (in the case of Columbia subjects) confirms the correct identity of patients via an interface with the electronic medical patient index. Staff with the appropriate IRB defined roles can run reports within the system for reporting purposes.

16.2. Data Reporting

Case Report Forms will be completed for each subject enrolled into the clinical study through the CTMS. It is the investigator's responsibility for ensuring that all clinical and laboratory data entered on the corresponding CRFs are complete, accurate and authentic.

16.3. Data and Safety Monitoring Committee

The NCI-approved Data Safety and Monitoring Committee (DSMC) of the Herbert Irving Comprehensive Cancer Center (HICCC) will monitor every subject who receives treatment on this protocol for toxicity. This protocol will adhere to the policies of the currently approved HICCC Data and Safety Monitoring Plan (DSMP), which is in accordance with NCI and CUMC-IRB policy and guidelines. The committee chair is appointed by the HICCC Director. The committee consists of HICCC faculty and staff with expertise in oncology, research pharmacy, research nursing, and data management. The DSMC convenes twice a month to review patient safety and the conduct of the trial. The PI will submit data and safety monitoring reports to the DSMC at a frequency to be determined by the DSMC based on risk to the subjects.

At the time of renewal, the study team will submit the most recent DSMC approval letter for safety review to the CUMC IRB. Any modifications that are required by the DSMC to ensure patient safety will be submitted to the IRB. All protocol deviations, violations, and eligibility waivers will be submitted to and approved by the DSMC prior to being reported to the IRB. All study data reviewed and discussed during these meetings will be kept confidential.

For multicenter research, the principal investigator will assure that there is a mechanism in place to distribute the report to all participating investigators for submission to their local IRB. The report will document that a review of data and outcomes across all centers took place on a given date. It will summarize the DSMC's review of the cumulative toxicities reported from all participating sites without specific disclosure by treatment arm. It will also inform site investigators of the study the DSMC's conclusion with respect to progress or need for modification of the protocol.

16.4. Quality Control and Quality Assurance

Independent monitoring of the clinical study for protocol and GCP compliance will be conducted periodically by the CPDM Compliance Core on behalf of the HICCC DSMC. Additionally, the Compliance Oversight Committee of the IRB at Columbia University Medical Center may audit the study at any time per institutional policies and procedures. The investigator-sponsor and Columbia University Medical Center will permit direct access of the study monitors and appropriate regulatory authorities to the study data and to the corresponding source data and documents to verify the accuracy of this data.

A risk-based approach will be used by the Compliance Core to determine the frequency, number of subject charts, and data elements to be monitored. The Compliance Coordinator will review the study status and summarize enrollment, toxicities, SAEs/UPs, dose escalation, statistical endpoints (e.g., stopping rules), etc. for the full DSMC membership at the regularly scheduled meetings.

Internal On-site Monitoring:

- Initial, recurrent, and close-out on-site monitoring visits will also be conducted at remote clinical sites, as appropriate/feasible. Other sites will have monitoring performed remotely (see below for further details).

- The study Monitoring Visit Log will be completed and signed by the monitor and the PI/CRNP/CRN and/or CRC and will be filed in the regulatory binder.

- The Compliance Coordinator will communicate with the site coordinator/Site Principle Investigator to schedule the monitoring visit and arrange for access to study materials and documentation.

- The assigned Compliance Coordinator will monitor IIT trials within 1 month after the first subject is enrolled and throughout the life of the study to ensure that the study is being conducted in accordance with the protocol, GCP, applicable federal and local regulations, and per all applicable SOPs. The Compliance Coordinator is responsible to notify the PI and CRNP/CRN/CRC of upcoming monitor visits and convey what information and documentation will be required for the visit(s). The Compliance Coordinator is responsible for verifying that informed consent is properly obtained, eligibility is met (via the central registration process), and all study procedures are conducted according to the study protocol. The Compliance Coordinator will also verify that the data reported in the CRF's accurately reflect source documents, that all toxicities have been reported to date, and that all SAE's/UPs/deviations/violations have been reported according to local IRB and HICCC DSMC requirements. The Compliance Coordinator will issue queries and ensure resolution in a timely and efficient manner. The Compliance Coordinator will also monitor for applicable regulatory compliance and research pharmacy compliance (if applicable) and communicate any deficiencies as appropriate.

16.5. Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (e.g., that the subject is alive) at the end of their scheduled study period.

The subject binders will be maintained with in the CPDM offices, a secured floor within the Herbert Irving Pavilion and only the investigator and study staff will have access to the file.

16.6. Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

16.7. Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A".

16.8. Records Retention

Records relating to a specific research activity, including research records collected by investigators, must be maintained for at least three years after completion of the research (45 CFR 46.115(b); 21 CFR 56.115(b); 21 CFR 312.62). This minimum retention period applies whether or not any subjects were enrolled in the study.

If the research is FDA regulated, records should be retained for at least two years after approval of the investigational agent by FDA; if it is not approved, records should be retained at least two years after the study is terminated and FDA is notified (note the additional requirement below for clinical research studies).

Clinical records, including consent forms that document clinical intervention or clinical diagnostic procedure research-related procedures, must be retained in medical records by the institution for at least seven years, per CUMC and NYP policy which is based on state law.

17. STATISTICAL CONSIDERATIONS

17.1. Study Endpoints and Analysis Plan

Definition of primary outcome/endpoint:
The primary endpoint is the overall response rate defined as the best response within the first 24 weeks of the start of study therapy using RECIST v. 1.1 that has been confirmed at a subsequent

time point (≥4 weeks).

Definition of secondary outcomes/endpoints:
PFS is defined as time from enrollment to time of clinical or radiographic disease progression as defined by RECIST v.1.1 criteria. OS is defined as time from enrollment to time of death from any cause.

Analytic plan for primary objective:
We will estimate the response rate to combination therapy with epacadostat and pembrolizumab using the exact 95% confidence interval based on the binomial distribution.

Analytic plan for secondary and exploratory objectives:

- We will estimate the survival distribution for both PFS and OS endpoints using the Kaplan Meier method. The log rank test will be used to examine differences between survival curves using prognostic markers such as KIT mutation status.
- For correlative studies we will apply either the Fisher's exact test or Wilcoxon rank sum test to examine the correlation between response status and markers for categorical and continuous variables, respectively. Because of the limited sample size, the biomarker data analysis is for exploratory research only.

Sample Size Justification
The primary endpoint of this trial is the objective response rate defined as the best response within the first 24 weeks of the start of study therapy using RECIST v1.1 criteria, and that has been confirmed at a subsequent time point (≥4 weeks).. We will use a Simon mini-max two-stage design with a target objective response rate of 20%, compared to a historical response rate of 5% with salvage tyrosine kinase inhibitor monotherapy[10], and the probabilities of type I and type II error set at 0.1 and 0.2 respectively. In the first stage, 12 patients will be accrued. If less than 1 patient achieves a response among the initial 12 patients, the study will be declared negative and terminated. If at least 1 patient achieves a response, an additional 9 patients will be accrued to the second stage for a total of 21 evaluable patients. If at least 3 total patients achieve a response, that treatment will be declared positive for attaining the primary endpoint. This study design yields at least 80% power to detect a 20% response rate (compared to the null hypothesis of 5%) at a significance level of 10%. There is a 54% chance of stopping at Stage 1 if the true confirmed response rate is at most 5% (null hypothesis). Accounting for 10% dropout, we will plan to enroll a total of 23 patients.

17.2. Stratification Factors

Not Applicable.

17.3. Reporting and Exclusions

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) will be included in the main analysis of the response rate. Patients in response categories 4-9 will be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate.

All conclusions should be based on all eligible patients. Sub-analyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these sub-analyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

18. PROTECTION OF HUMAN SUBJECTS

This study is to be conducted in accordance with applicable government regulations and Institutional research policies and procedures. An IND annual report will be submitted to the FDA in accordance with 21.CFR 312.33.

This protocol and any amendments will be submitted to a properly constituted Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be obtained before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, as outlined in the IRB approved protocol, and the investigator-designated research professional obtaining the consent.

19. STUDY FINANCES

19.1. Conflict of interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the Columbia University Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved prior to participation in this study. All CUMC investigators will follow the University conflict of interest policy.

19.2. Subject Stipends or Payments

There are no subject stipends or payments.

20. PUBLICATION PLAN

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

21. GUIDELINES FOR AFFILIATE INSTITUTIONS IN MULTICENTER STUDIES

21.1. Multi-site Communication

The CPDM Office at CUMC provides administration, data management, and organizational support for the affiliate sites in the conduct of a multicenter clinical trial. The CPDM Office will coordinate regularly scheduled conference calls with affiliate sites.

The following issues will be discussed, as appropriate:

- Enrollment information
- Response assessments
- Adverse events (e.g., new adverse events and updates on unresolved adverse events and new safety information)
- Protocol violations
- Other issues affecting the conduct of the study

21.2. New Protocol Distribution, IRB Submission, Modifications, and Annual Renewals

- Protocol specific documents are distributed to affiliate sites once CUMC IRB approval has been obtained.
- The affiliate site must submit a draft of site specific revisions to protocol and/or consent form documents for review and approval by the sponsor-investigator prior to submission to the local IRB. Draft documents should be sent to the study specific email

address. The site will be provided confirmation that they are approved to submit to their local IRB.

- Protocol amendments must be approved by the affiliate site's local IRB within 90 days of distribution to the site by the sponsor-investigator.

21.3. Regulatory Documents

Prior to Site Initiation:
Sponsor-Investigator will ensure that proper requests are made of sites and that the following documentation is collected, prior to the initiation of an affiliate site.

- CV of PI, Co-I's and other research staff listed on FDA 1572 (signed and dated copy within 2 years)
- Medical Licenses of PI and Co-I's (current copy)
- Human subjects training certificates for PI and Co-I's
- CLIA/Laboratory Certifications for Local Laboratories listed on FDA 1572
- Local Laboratory Director's CV and License
- Local Laboratory Reference Ranges
- IRB roster or statement of compliance
- FDA Form 1572, if applicable (wet ink originals required)
- Financial Disclosure forms for all members listed on FDA 1572 (wet ink originals required)

Ongoing Regulatory Documentation: Sponsor-Investigator will ensure that proper requests are made of sites and that the following documentation is collected throughout the course of the study.

- IRB approval letters for all protocol modifications and all renewals
- IRB-approved consent forms
- Current IRB roster, if statement of compliance is not provided as part of site initiation
- FDA Form 1572, if applicable as updates are required
- Updated investigator and site information where relevant (e.g., CV, medical licensure and Financial Disclosure for new sub-investigator, local laboratory information)

Regulatory documents may be sent to CPDM_R1581@lists.cumc.columbia.edu or to the following address:

Clinical Protocol & Data Management Office
161 Fort Washington Ave.
Herbert Irving Pavilion
Mezzanine Level, M-203
New York, NY 10032

21.4. Site activation

Columbia University will schedule a site initiation visit once IRB approval has been submitted from the affiliate site.

21.5. Central Registration Procedures- Affiliate Institution Research Participant Registration Process

All Affiliate Institutions **must** register subjects with the coordinating center (CUMC) **prior** to any administration of study drug/intervention/local institution registration. Please see instructions below:

1. Within 48 hours of obtaining consent (excluding holidays and weekends), the Affiliate Institution CRN and/or CRC is required to submit the following documents to the coordinating center's designee (CUMC Multicenter Core) via the study listserv CPDM_R1581@lists.cumc.columbia.edu. The coordinating center's designee will review the documents for accurateness, and subsequently submit the documents to the CPDM Central Registration Office via email at CPDMRegistration@columbia.edu (or via fax at 212.305.5292), with a request to register the patient "pending eligibility." The title of the email should read, "Pending Subject Registration Request (PHI)". The following documents should be submitted with the pending registration request, as applicable:
    a. Redacted Completed/signed IRB approved/stamped Informed Consent Forms, including additional study ICFs (e.g., tissue, DNA, etc.), as applicable
    b. Redacted Signed HIPAA (or institutional equivalent)
    c. MCT CPDM Velos Note to File form

2. The Affiliate Institution's investigator/research nurse/data manager/coordinator must contact the coordinating center's designee (CUMC Multicenter Core) via telephone or email to communicate the following:
    a. Notify of pending registration request
    b. Confirm method of registration request submission (email or fax)
    c. Communicate expected time-line of registration request submission (e.g., same day, next day, within the hour, etc.)

3. To complete registration, the Affiliate Institution's investigator/research nurse/data manager/coordinator should then submit the following documents to the CUMC study specific designee:
    a. A signed Affiliate Site Eligibility Checklist (signed by the investigator)
    b. Copies of redacted source documentation necessary for each item to be verified on the CUMC specific Eligibility Checklist, including but not limited to:
        i. Copy of required laboratory test and procedure reports (e.g., hematology, serum chemistry, pregnancy test when applicable, MRI reports, CT/bone scans, etc.)
        ii. Copy of pathology and surgical reports
        iii. Copy of clinic note(s) capturing the consent process information, along with providing source documentation of any other items needed for screening/eligibility that are not captured in other source document forms.

(e.g., positive investigator statements of unique eligibility items not captured via other direct source documentation, concomitant medication lists, etc.)

iv. Protocol deviation/waiver approvals (if applicable)

c. **Please note**: subject line of email or fax should include the following: "AAAR1581 Complete Subject Registration Request (PHI)".

4. Upon receipt of the above mentioned documents, the designated study specific Clinical Research Coordinator will review all documents and verify patient eligibility. If any questions arise during the review process, queries in the form of emails will be addressed to the applicable affiliate site study team personnel for clarification prior to enrollment. Upon verification, the CUMC Multicenter Core will then forward all documents to the CPDM Central Registration Office for central registration (as described above). The CPDM Central Registration Registrar will review all applicable documents and communicate to the CUMC study specific designee in order to clarify any items. The CUMC study specific designee will communicate with the applicable site study team personnel for additional clarifications necessary prior to enrollment.

5. Upon receipt of the subject registration notification email, the CUMC Multicenter Core will forward the notification email (which will include the study specific patient ID) to the affiliate site's Principal Investigator, Consenting Professional, and applicable research personnel. This notification should be filed in the patient research binder accordingly. Protocol therapy **may not** be initiated prior to receipt of this notification from the coordinating center.

6. All screenfail/ineligible subjects, as well as subject's who withdraw consent prior to enrollment/initiation of protocol therapy must be submitted to the Central Registration Office in a manner analogous to the procedures noted above. Applicable source documentation will be required within the corresponding submissions.

21.6. Protocol Deviation/Subject Waiver request for Affiliate Sites:

The Affiliate site MUST submit a prospective deviation request to the CUMC lead PI for review and submission to the HICCC DSMC and CUMC IRB. Approvals must be obtained from all entities prior to implementation at the Affiliate site. If a prospective protocol deviation request is submitted for review (from an Affiliate site), the PI/site memo(s), HICCC DSMC approval(s) and correspondence and CUMC IRB approval letter(s)/equivalent should be forwarded to the Affiliate site for documentation. The Affiliate site is also required to obtain prospective local IRB approval as per institutional policies/procedures prior to implementing the proposed deviation and registering/enrolling the subject via CUMC Central Registration. All documents and determinations must be clearly documented in the study subject's medical record, research chart and regulatory binder, as described. Please note that the HICCC DSMC and PRMC do not approve eligibility deviations. If eligibility deviations are submitted, they will not be approved.

21.7. Guidelines for Affiliate Site Monitoring

On-Site MCT Monitoring:

1. Initial, recurrent, and close-out on-site monitoring visits will also be conducted at Affiliate sites, as appropriate/feasible. Other sites will have monitoring performed remotely (see below for further details).
    a. The study Monitoring Visit Log will be completed and signed by the monitor and the PI/CRNP/CRN and/or CRC and will be filed in the regulatory binder.
2. The Compliance Coordinator will communicate with the Affiliate site coordinator/Site Principle Investigator to schedule the monitoring visit and arrange for access to study materials and documentation.
3. The Compliance Coordinator will monitor IIT trials within 1 month after the first subject is enrolled at the Affiliate site and throughout the life of the study to ensure that the study is being conducted in accordance with the protocol, GCP, applicable federal and local regulations, and per all applicable SOPs. The Compliance Coordinator is responsible to notify the participating site PI and CRNP/CRN/CRC of upcoming monitor visits and convey what information and documentation will be required for the visit(s). The Compliance Coordinator is responsible for verifying that informed consent is properly obtained, eligibility is met (via the central registration process), and all study procedures are conducted according to the study protocol. The Compliance Coordinator will also verify that the data reported in the CRF's accurately reflect source documents, that all toxicities have been reported to date, and that all SAE's/UPs/deviations/violations have been reported according to Coordinating Center, local IRB and HICCC DSMC requirements. The Compliance Coordinator will issue queries and ensure resolution in a timely and efficient manner. The Compliance Coordinator will also monitor for applicable regulatory compliance and research pharmacy compliance (if applicable) and communicate any deficiencies as appropriate.

4. An SIV (or) teleconference will be scheduled and conducted prior to study drug being made available (if applicable) and before any subjects are enrolled on a study at the Affiliate site.

Remote MCT Monitoring:

- When necessary (due to logistical constraints), Affiliate sites will be monitored remotely by a designated Compliance Coordinator. Sites will be informed of this remote monitoring process on a site by site basis.
- Affiliate sites will be monitored by the Compliance Coordinator on both a regulatory level, as well as a clinical data/source documentation review level.
- Redacted source documents (applicable to supporting the protocol specific CRF data requirements) will be sent to the designated Compliance Coordinator via fax or secure email for all subjects enrolled at Affiliate sites. Timelines for submission procedures will be defined on a case by case basis.
- The Compliance Coordinator will review all submitted redacted source documents against the data entered on the protocol specific CRFs. The Compliance Coordinator will issue queries when/if necessary.

- The Affiliate site research staff will respond to queries within 30 days. If queries remain outstanding, the Compliance Coordinator will send a delinquent query reminder for the outstanding items.
- The remote monitoring procedures will include review of applicable redacted source documentation and supporting applicable documents to determine compliance regarding:
    a. Informed consent procedures
    b. Eligibility criteria
    c. Protocol specific treatment compliance
    d. Protocol specific toxicity/outcome documentation/compliance
    e. Protocol specific schedule of events (e.g., baseline visits, pre-treatment, on study, follow-up)
    f. Participating site IRB documents (e.g., IRB amendment approvals, annual renewals, SAE/UP submissions, violation/deviation submissions, INDSR submissions, etc).
    g. Required specimen submissions (e.g., tissue specimens, research blood specimens, etc.)
    h. Pharmacy accountability records
    i. Adherence to the CRF submission timeframes to CUMC (within the protocol specified timeframes)
- Affiliate site remote monitoring reports will be sent to the lead PI, HICCC DSMC, and Affiliate sites after each remote monitoring review. Reports will include information regarding data submission timeliness/accuracy, protocol adherence items, query resolution status, regulatory status, and overall Affiliate site performance. These reports will be generated by the Compliance Coordinator and reviewed with the Compliance Core Manager prior to dissemination.

21.8. Adverse event reporting

Sponsor reporting: Notifying participating investigators at affiliate sites of adverse events

It is the responsibility of the study sponsor to notify all affiliate sites, in a written IND safety report, of any adverse event associated with the use of the drug that is both serious and unexpected, as well as any finding from tests in laboratory animals that suggest a significant risk for human subjects. Additionally, sponsors are also required to identify in IND safety reports all previous reports concerning similar adverse events and to analyze the significance of the current event in light of the previous reports.

Serious Adverse Event Reporting

Each participating investigator is required to abide by the reporting requirements set by Columbia University Medical Center. The study must be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the principal investigator.

Participating investigators must report each serious adverse event to the Columbia University Medical Center Overall Principal Investigator within 24 hours of learning of the occurrence using

the SAE Report Form. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the adverse event. Report serious adverse events by telephone, email or facsimile to:

Richard D. Carvajal, MD
177 Fort Washington Avenue
New York, NY 10032
Telephone: 212-305-2055
Fax: 212-305-3035
Email: CPDM_R1581@lists.cumc.columbia.edu

Within the following 24-48 hours, the participating investigator must provide follow-up information on the serious adverse event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

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

If the SAE is not previously documented in the Investigator's Brochure for the study drug (new occurrence) and is thought to be related to the investigational agent, the sponsor-investigator may urgently require further information from the investigator for reporting to Health Authorities.

Non-Serious Adverse Event Reporting

Non-serious adverse events will be reported to the Columbia University Medical Center Overall Principal Investigator on the toxicity Case Report Forms.

Reporting to the Institutional Review Board (IRB) and the Data and Safety Monitoring Committee:

All Unanticipated Problems (UPs) will be reported to the CUMC IRB. SAEs not constituting UPs will reported to the HICCC DSMC.

Each affiliate site will be responsible for safety reporting to their local IRB. Investigators are responsible for complying with their local IRB's reporting requirements, though must submit the required reports to their IRB no later than 7 calendar days following the occurrence of the UP or the Principal's Investigator's acquiring knowledge of the UP. Copies of each report and documentation of IRB notification and receipt must be included in the regulatory binder.

Expected or unexpected AEs must be reported at the time of continuing review of a protocol.

Guidelines for Processing IND Safety Reports

The U.S. Food and Drug Administration (FDA) regulations require sponsors of clinical studies to notify the FDA and all participating investigators of any serious and unexpected adverse experiences that are possibly related to the investigational agent. The CUMC Principal Investigator will review all applicable IND Safety Reports and has the responsibly for forwarding the IND Safety Reports to the Affiliate Institutions. The Affiliate Institution investigators are to review, send a copy to their IRB according to their local IRB's policies and procedures, and file a copy with their regulatory documents. All Affiliate site INDSR submissions, along with IRB acknowledgment (per local policies and procedures) are to be forwarded to CUMC for placement within the trial master file.

Reporting to Hospital Risk Management

Affiliate Site investigators will report to their local Risk Management Office any subject safety reports or sentinel events that require reporting according to institutional policy.

21.9. Efficacy analysis/ correlative analysis

Efficacy analysis:
CT scans will be reviewed by a site radiologist and interpreted according to response criteria detailed in section 12.4 for primary and secondary endpoint analysis. Imaging studies may be requested from participating centers for central radiology review.

Correlative analysis:
All tissue samples collected at each site will be sent to Columbia University Medical Center for storage and correlative studies described above.

21.10. Confidentiality

Each affiliate site will be assigned a site number. Each subject that signs consent should be assigned a unique code number consisting of site number followed by a number with each new subject being assigned the next sequential number (e.g., 04-10). All sites will be required to enter their data in the Velos eResearch, the Clinical Trial Management System used for all Cancer-related clinical research at CUMC. All users must login with their own application username and password. Users off campus must first access the Virtual Private Network with their assigned campus username and password and then use their application credentials.

Subject confidentiality must be maintained according to HIPAA regulations and GCP recommendations.

Except when required by law, study information shared with persons and organizations outside of

Columbia University Medical Center must not identify the patient by name, social security number, address, telephone number, or any other direct personal identifier.

If the results of this research project are published or presented at a scientific or medical meeting, the patient not be identified. Otherwise, all results will be kept confidential and will not be divulged (except as required by law) without permission.

21.11. Data Reporting Plan

Columbia University Medical Center (CUMC) is deeply committed to research integrity and strong credibility when it comes to the discovery of new treatment concepts, implementation of new clinical research techniques, and acceptance of its researcher's findings by the medical establishment. In accord with these ethics, CUMC encourages and supports its investigators in the sharing of final research data and/or details of newly developed clinical treatments.

CUMC's policies that pertain to patient data sharing conform to CUMC IRB rules, local and state laws, and HIPAA privacy regulations. The primary reason for this is to protect the privacy of patients who participate in clinical trials. The data can be made available for continuing review by federal agencies upon request and for ongoing study safety reviews by the Principal Investigator, Statistician, Data Safety and Monitoring Board (DSMC), and, in other instances, the CUMC IRB.

Data collected during the course of this clinical trial will primarily be shared with other investigators and University staff, the IRB, FDA, and other reporting agencies, and/or transferred to other collaborators. Prior to transfer, the data collected must comply with, and must be limited by, the CUMC's guidelines for Protecting the Rights and Privacy of Human Subjects.

21.12. Data Acquisition and Submission

Informed consent, including HIPPA authorization, must be obtained on all subjects prior to their participation. Always keep the original signed and dated consent form, with the redacted source documents and eligibility checklist. Velos eResearch will be used as the electronic clinical trials and data management system. Affiliate sites will enter data directly into Velos eResearch via customized case report forms for the study. The research staff will generate reports from Velos eResearch to ensure timely submission of data by affiliate sites. This resource allows for the timely analysis of particular data sets for safety analysis.

21.13. Record Keeping and Record Retention

The Principal Investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects, as well as written records of the disposition of the drug when the study ends.

The Principal Investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories

include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.
Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, CHR correspondence and approval, signed patient consent forms).
Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.
In accordance with FDA regulations, the investigator shall retain records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

22. REFERENCES

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23. APPENDIX

23.1. Appendix A: ECOG Performance Status Criteria.

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

23.2. Appendix B: Appropriate contraceptive methods for study subjects.

The following methods have been determined to be more than 99% effective (<1% failure rate per year) when used consistently and correctly[35] and are permitted under this Protocol for use by the subject and his/her partner:

- Complete abstinence from sexual intercourse
- A barrier method (male or female condom) in addition to one of the following:
    - Diaphragm or cervical cap with spermicide
    - Intrauterine device (IUD)
    - Birth control patch or vaginal ring
    - Oral, injectable, or implanted contraceptives

23.3. Appendix C: Prohibited Monoamine Oxidase Inhibitors (MAOi) and Drugs Associated with Significant MAOi Activity.

Monoamine Oxidase Inhibitors (MAOi)	Drugs Associated with Significant MAOi Activity
Hydrazines (ex: phenelzine)	Meperidine
Caroxzone	Linezolid
Echinopsidine	Methylene blue
Furazolidone	
Tranylcypromine	
Brofaromine	
Metralindole	
Minaprine	
Moclobemide	
Pirlindole	
Toloxatone	
Lazbemide	
Pargyline	
Rasagiline	
Selegiline	

23.4. **Appendix D:** Pill Diary

Name:_____ Date: _____ Study ID/ MRN: _____

Medication Diary for: A Phase II Study of Epacadostat (IDO inhibitor) and Pembrolizumab in Patients with Imatinib-Refractory Advanced Gastrointestinal Stromal Tumors

Number of Capsules/Tablets Given
Epacadostat: _____

Medication Bottle(s) returned: Circle **Yes** or **No**
Number of Capsules/Tablets returned
Epacadostat: _____

Total Daily Dose ***(To be Completed by RN)***
Epacadostat: _____

PLEASE FILL OUT AND BRING THIS SHEET AT YOUR NEXT VISIT.

- Please take dose of Epacadostat by mouth twice daily. Please allow for adequate time (approximately 12 hours) between your AM and PM dosing time and record below. You are encouraged to remain consistent with your daily dosing schedule throughout your treatment. Do not chew the capsules.
- Any dose missed or vomited should not be replaced.
- If you forget a dose but within 4 hours of its scheduled administration time, you should take it; if more than 4 hours have passed, note as dose missed and continue treatment with the next scheduled dose.
- Study Medication can be taken without regard to food (i.e., study medication can be taken with or without food).
- Please store study medications at room temperature.
- Please bring this diary with you to each appointment.

CYCLE #: _____ # of WEEKS_____

DAY	**DATE**	**TIME**			**NUMBER of XXmg capsules taken**
Example	**01/01/2010**	**9:00**	**AM**	**Epacadostat**	**1 100mg tablet taken**
		9:00	**PM**	**Epacadostat**	**1 100mg table taken**
Day 1			**AM**	**Epacadostat**	
			PM	**Epacadostat**	

Day 2			**AM**	**Epacadostat**	
			PM	**Epacadostat**	
Day 3			**AM**	**Epacadostat**	
			PM	**Epacadostat**	
Day 4			**AM**	**Epacadostat**	
			PM	**Epacadostat**	
Day 5			**AM**	**Epacadostat**	
			PM	**Epacadostat**	
Day 6			**AM**	**Epacadostat**	
			PM	**Epacadostat**	
Day 7			**AM**	**Epacadostat**	
			PM	**Epacadostat**	
Day 8			**AM**	**Epacadostat**	
			PM	**Epacadostat**	
Day 9			**AM**	**Epacadostat**	
			PM	**Epacadostat**	

Day 10			**AM**	**Epacadostat**	
			PM	**Epacadostat**	
Day 11			**AM**	**Epacadostat**	
			PM	**Epacadostat**	
Day 12			**AM**	**Epacadostat**	
			PM	**Epacadostat**	
Day 13			**AM**	**Epacadostat**	
			PM	**Epacadostat**	
Day 14			**AM**	**Epacadostat**	
			PM	**Epacadostat**	
Day 15			**AM**	**Epacadostat**	
			PM	**Epacadostat**	
Day 16			**AM**	**Epacadostat**	
			PM	**Epacadostat**	
Day 17			**AM**	**Epacadostat**	
			PM	**Epacadostat**	

Day 18			**AM**	**Epacadostat**	
			PM	**Epacadostat**	
Day 19			**AM**	**Epacadostat**	
			PM	**Epacadostat**	
Day 20			**AM**	**Epacadostat**	
			PM	**Epacadostat**	
Day 21			**AM**	**Epacadostat**	
			PM	**Epacadostat**	

Patient Signature: _____Date: _____

Research RN Signature: _____Date: _____

Research RN Comments:_____