MSKPROTOCOLCOVERSHEET

Phase II Study of Epacadostat (INCB024360) in Combination with Pembrolizumab in Patients with Locally Advanced/Metastatic Sarcoma

Principal Investigator/Department: Sandra P. D' Angelo, MD/ Medicine

Table of Contents

1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Sarcomas comprise a very diverse group of malignancies including more than 50 subtypes of bone and soft tissue origin. Despite optimal approach, approximately 30-80% of patients will develop recurrent and metastatic disease after receiving initial therapy with curative intent. In this setting, responses to standard cytotoxic chemotherapy occur in 10-30% of the cases and median survival is 10-18 months.

Sarcomas are immunogenic neoplasms with a need for more therapeutic options. Prior immunotherapeutic agents have shown promise in select sarcoma patients. Using a combination of epacadostat, an IDO-1 inhibitor administered concurrently with the anti-PD1 monoclonal antibody pembrolizumab to treat patients with sarcomas and our planned scientific correlates, we believe we can assess the safety and efficacy of immune activating therapy and better understand the effects of combined therapy in antitumoral immune response.

This is an open-label, single-center, phase II study to evaluate the efficacy of epacadostat in combination with pembrolizumab in patients with locally advanced/metastatic, grade sarcoma (Figure 1. Study Schema). One treatment cycle will consist of 21 days. Patients will start both study drugs on day one of the first cycle. They will receive epacadostat 100mg, orally, twice daily, continuously for 21 days (Table 1). They will receive 200mg of pembrolizumab intravenously on day 1 of every three week cycle (Table 1). Patients will be reassessed with CT scans at week 8 and every 8 weeks thereafter. Treatment will be repeated until the patient develops progressive disease or unacceptable toxicity.

A total of 30 patients will be enrolled onto the study. Patients will be enrolled onto one of 4 cohorts. Each cohort will enroll a prespecified number of patients with certain sarcoma histological subtype(s). The 4 patient cohorts and the number of patients eligible to enroll per cohort in this study are as follows:

A) Undifferentiated Pleomorphic Sarcoma (UPS), Liposarcoma (dedifferentiated or pleomorphic liposarcoma), or Myxofibrosarcoma (n=10)

B) Leiomyosarcoma (n= 5)

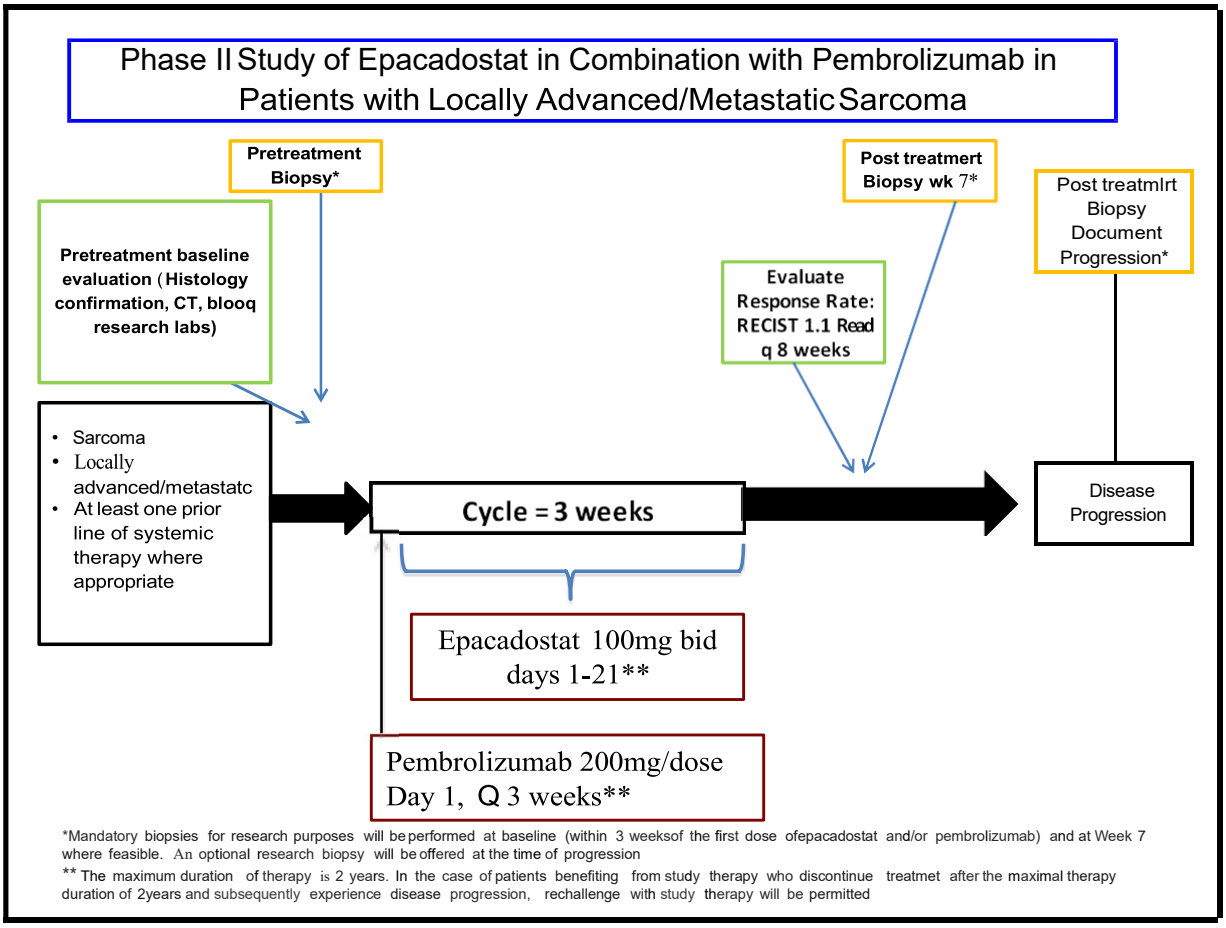
C) Vascular Sarcoma Subtypes (includingangiosarcoma ,and Epithelioid Hemangioendothelioma (EHE)) (n=5)

D) Other (n=10)

Table 1 Study Treatment

Study Drug	Dose	Dose Frequency	Regimen/Treatment Period	Route of Administration
Epacadostat	100mg	Twice daily	Continuously days 1-21 of each 3 week cycle	Oral
Pembrolizumab	200mg	Every 3 weeks	Day 1 of each 3 week cycle	IV infusion

Figure 1. Study Schema



The hypotheses for this study include:

Primary hypothesis

1. Epacadostat given in combination with pembrolizumab, will ellicit an enhanced immune response in patients with advanced sarcoma with antitumoral effect, as assessed by RECIST 1.1.

Secondary hypotheses

1. Epacadostat, given in combination with pembrolizumab will be safe and well tolerated in patients with advanced sarcomas.

2. Epacadostat, given in combination with pembrolizumab, will improve progression free survival and overall survival in patients with advanced sarcoma as assessed by RECIST 1.1 and irRECIST.

3. Epacadostat, given in combination with pembrolizumab, will ellicit an enhanced immune response in patients with advanced sarcoma with antitumoral effect, as assessed by irRECIST.

Exploratory hypotheses

1. Baseline characteristics of the immune micorenvironment of sarcoma tumor tissue will vary depending on the sarcoma histological subtype.
2. Epacadostat given in combination with pembrolizumab, will alter immune related characteristics of tumor tissue in ways that may correlate with clinical outcome.
3. Epacadostat given in combination with pembrolizumab, will alter immune related characteristics of peripheral blood in ways that may correlate with clinical outcome
4. Epacadostat, given in combination with pembrolizumab, will benefit a substantial portion of patients with advanced sarcomas. Baseline tumor mutational burden and neoantigen production and and patient-specific immune characteristics,may correlate with clinical efficacy of the study therapy

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objective:

To evaluate the efficacy of epacadostat in combination with pembrolizumab in patients with advanced sarcoma, as assessed by the best objective response rate (complete response+ partial response) by 24 weeks using RECIST 1.1.

Secondary Objectives:

1) To assess the safety of epacadostat in combination with pembrolizumab in patients with advanced sarcoma using CTCAE v4.03 criteria for toxicity assessment.

2) To determine the progression free survival (PFS) rate at 24 weeks by RECIST 1.1 and irRECIST and overall survival (OS) for patients treated with epacadostat in combination with pembrolizumab.
3) To evaluate the efficacy of epacadostat in combination with pembrolizumab in patients with advanced sarcoma, as assessed by the best objective response rate (complete response + partial response) by 24 weeks by immune-related response evaluation criteria in solid tumors (irRECIST).

Exploratory Objectives:
i) To determine the baseline characteristics of sarcoma tumors (pre-treatment biopsy sample) evaluated in this study including the level of IDO1, kynurenine and PD-1/PD-L1 expression, presence of tumor infiltrating lymphocytes (TIls) and tumor antigens, gene expression profile, and the T-cell receptor clonality in tumor-infiltrating lymphocytes (TIL).

ii. To assess the potential effect of epacadostat and pembrolizumab on selected biomarker expression measured in pre- and post-treatment tumor tissue and the association between these biomarkers (baseline level of expression and the change in biomarker level of expression following treatment) and clinical outcome, including characterization of IDO-1 expression, PD-1/PD-L1 expression, kynurenine expression, tumor infiltrating lymphocytes (TIls) and tumor antigens, gene expression profiling, and characterization of T-cell receptor clonality in tumor-infiltrating lymphocytes (TIL).

iii. To evaluate associations between selected biomarkers measured in serial peripheral blood and with clinical efficacy, including immunophenotyping and functional analyses, evaluation of serum levels of chemokines, cytokines and other immune mediators, and characterization of T-cell receptor clonality in peripheral blood.

iv. To evaluate the association between baseline tumor mutational burden and neoantigen production with clinical efficacy of the study therapy.

3.0 BACKGROUND AND RATIONALE

Sarcomas: New therapies are desperately needed

Sarcomas represent a collection of rare, heterogeneous tumors of mesenchymal origin. There are more than 50 distinct sarcoma subtypes. Approximately 13,000 patients are diagnosed with bone and soft tissue sarcomas every year in the United States. Surgery is the cornerstone of treatment for patients with localized, resectable sarcomas. Adjuvant radiation and chemotherapy are considered in very particular situations. However, despite combined modailty treatment 25-50% of patients develop a recurrence and/or metastatic disease.[1,2] The median survival for patients with metastatic sarcoma is 10-15 months.[3,4] Standard cytotoxic chemotherapy agents such as doxorubicin, ifosfamide, and dacarbazine result in objective responses in 10-30% of the patients, and this is significantly influenced by

histologic variant.[5] The development of novel and effective therapies is desperately needed for patients with advanced/metastatic sarcomas.

Sarcoma: an immunogenic tumor

Immunotherapeutic strategies may be a promising approach to treating this disease. The role of the immune system as a mechanism of cancer therapy was first observed in a sarcoma patient who had a response after an erysipelas infection.[6] Sarcomas are more common in patients who are immunosuppressed.[7] Infiltration of lymphocytes has been demonstrated in sarcomas.[8] Furthermore, tumor-infiltrating lymphocytes have been associated with improved survival in Ewing's sarcoma and GIST.[9-11] Spontaneous regression of primary tumors has been seen in desmoid tumors and osteosarcomas.[12,13] There have been multiple clinical trials evaluating the role of immune stimulants such as IL-2, interferon, and liposomal-muramyl tripeptide phosphatidylethanolamine showing some benefit in sarcoma patients.[14-18] T cells genetically engineered to target NY-ESO-1 expressing synovial sarcoma have shown some promise.[19] In patients with GIST, tyrosine kinase inhibitors such as imatinib can have stimulating effects on multiple immune cells.[11]

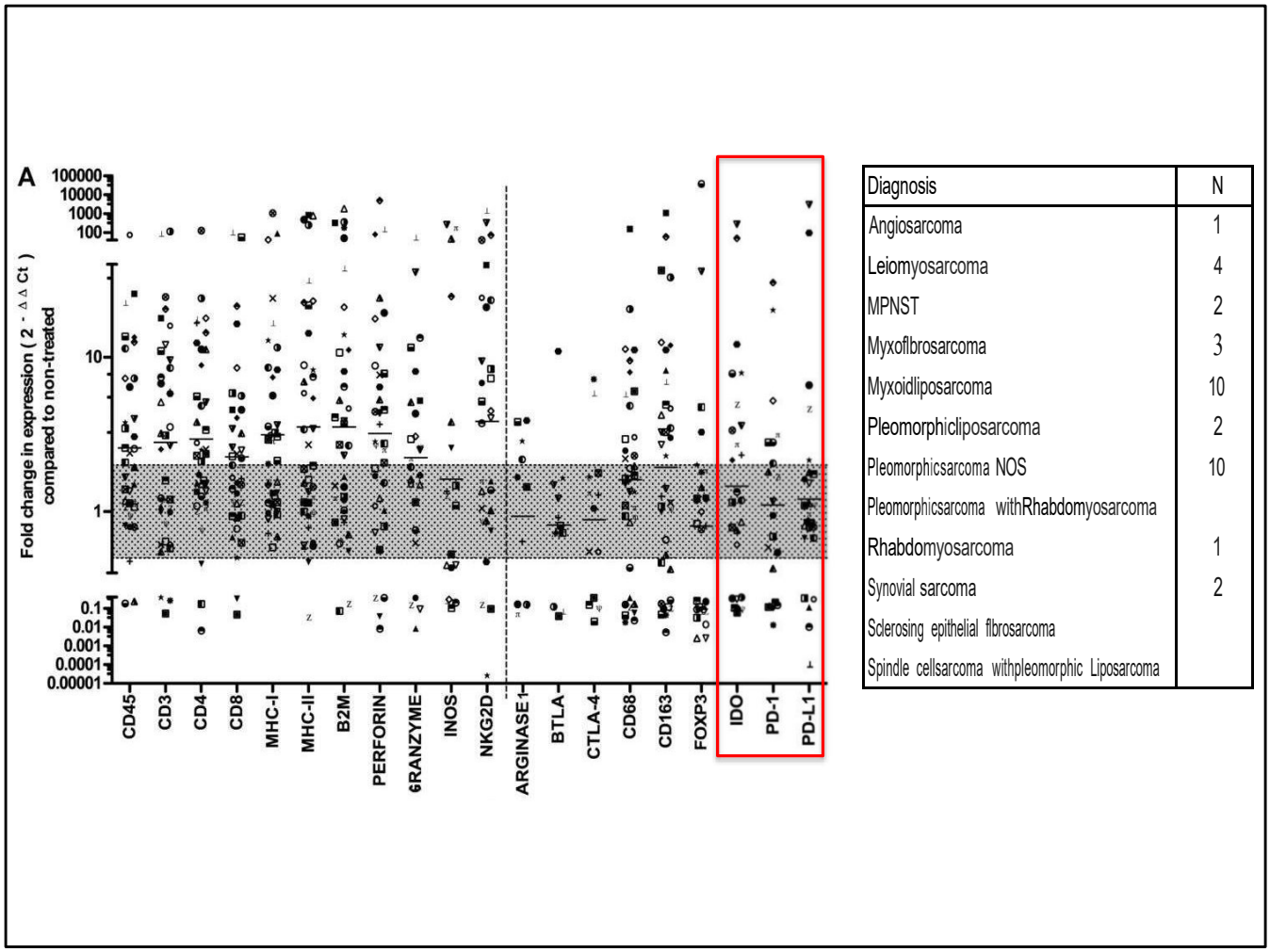
Immunotherapy in Sarcoma

The results of two clinical trials evaluating the efficacy of single agent PD-1 blockade in the setting of advanced sarcoma were recently presented in 2016 at the annual meeting of the American Society of Clinical Oncology. The first trial, a phase II study investigated the role of pembrolizumab in patients with patients with advanced soft tissue and bone sarcomas. A signal of efficacy for pembrolizumab monotherapy was observed in patients with undifferentiated pleomorphic sarcoma, liposarcoma, osteosarcoma and chondrosarcoma. However, no efficacy was observed in other subtypes such as leiomyosarcoma, synovial sarcoma and ewing's sarcoma.[20] Nivolumab monotherapy was also deemed to be ineffective in the setting of patients advanced uterine leiomyosarcoma.[21] Immunotherapy research efforts in sarcoma are now focusing on combination immunotherapy strategies.

Sarcoma: Microenvironment Immune Infiltrate is Susceptible to Manipulation

The sarcoma microenvironment is a critical factor that contributes to tumor growth and progression. Sharma A, et al, demonstrated this point when they retrospectively analyzed the expression of immune response-related genes by quantitative RT-PCR and immunohistochemistry on paired tumor samples taken before and after radiotherapy from 38 patients with sarcoma.[22] They observed that radiotherapy caused up-regulation of transcripts specific for several immune effector cells and concomitantly resulted in down regulation of various transcripts related to immune suppression including IDO1, PD-1 and PD-L1 in many patients. (Figure 2) They validated their findings at the protein level using immunohistochemistry by demonstrating that radiotherapy increased the expression of CT-antigens, MHC-I and lymphocyte infiltration. They also demonstrated that patients with prolonged survival greater than 3 years after radiotherapy had a clear down regulation of

genes associated with immune suppression compared to patients who died within three years of radiation therapy. This supports the hypothesis that radiotherapy promotes a durable protective immunity within the tumor microenvironment. This study importantly highlights the susceptibility of the sarcoma microenvironment to manipulation, particularly with respect to the immune infiltrate.



Diagnosis	N
Angiosarcoma	1
Leiomyosarcoma	4
MPNST	2
Myxoflbrosarcoma	3
Myxoidliposarcoma	10
Pleomorphicliposarcoma	2
Pleomorphicsarcoma NOS	10
Pleomorphicsarcoma withRhabdomyosarcoma	
Rhabdomyosarcoma	1
Synovial sarcoma	2
Sclerosing epithelial fibrosarcoma	
Spindle cellsarcoma withpleomorphic Liposarcoma	

Figure 2: Radiotherapy-induced changes of immune response-related gene expression in human sarcoma - Thirty-seven paired FFPE sarcoma samples before/after radiotherapy were subjected to qR-PCR analysis for 35 different immune response-related genes. Genes displayed on the left side of the vertical dotted line are associated with immune effectors and those on the right with immune suppressors. Each symbol represents an individual patient.

Indolamine 2, 3-dioxygenase (ID01)

ID01 is a rate-limiting, intracellular enzyme responsible for oxidation of tryptophan into kynurenine. ID01 activity reduces tryptophan that starves cytotoxic T-cells within the tumor microenvironment and causes their arrest in the G1 phase of the cell cycle.

Tryptophan metabolites activate regulatory T-cells, which further suppresses the immune response to the tumor enabling the tumor to evade the immune system.[23] (Figure 3)

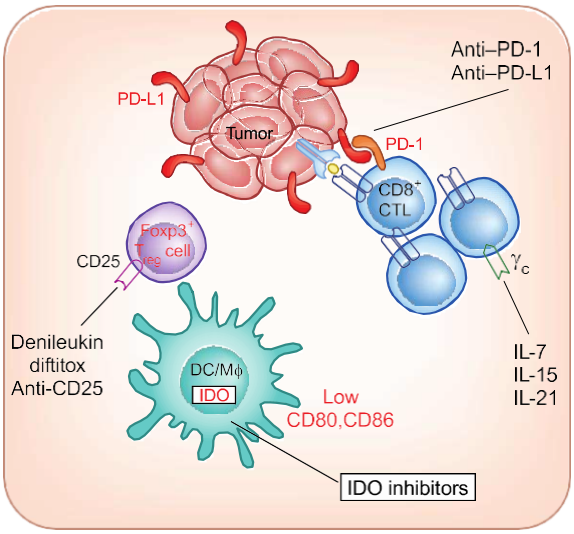


Figure 3: ID01 is one of several immune checkpoints involved in tumor immune escape. The ID01 enzyme, activated in dendritic cells (DC) and macrophages (Mcj>), helps create an environment that favors suppression and tolerance.

A study in melanoma has shown that infiltrating COB+ T cells elicit several immunosuppressive effects within the tumor microenvironment, including upregulation of 1001 and of PD-L1.[24] 1001 acts as a critical molecular switch driving mature, quiescent Tregs into diametrically opposite functional states. In the setting of a stimulated innate immune response 1001 is active and Tregs are maintained in their normal potently suppressive state. However, when 100 is blocked, Tregs undergo an inflammation-induced, IL-6 dependent conversion into a proinflammatory phenotype similar to effector, T-helper-17 cells.[22,25] 1001 inhibition increases and restores proliferation and activation of immune cells; including dendritic cells, NK cells, and T-lymphocytes, IFN production and causes a reduction in tumor associated regulatory T cells. A combination of 1001 inhibition and stimulation of the immune system through anti-PD1 and PD-L1 therapies may inhibit the growth of 1001 expressing tumors by manipulating the tumor microenvironment from an immune-suppressive state towards an immune activated state.

ID01 in Sarcoma:

In the setting of human sarcoma, Uyttenhove et al demonstrated 1001 expression in 20% of the sarcoma cell lines evaluated.[23] Vanderstraeten et al, determined 14% of uterine sarcomas (n=22) to express a high level of 1001.[26] Another study has shown 1001

expression levels as high as 41% in tumor cells of soft tissue sarcoma specimens. There was significant consistency in the joint expression of POL1 and IDO on tumor cells, POL1 and kynurenine, and kynurenine and IDO on tumor cells, in 70% ($p<0.0001$), 53% ($p=0.0004$) and 53% ($p=0.05$) of samples, respectively.[27] The level of IDO1 expression has also been evaluated in 47 patients with high grade osteosarcoma arising from an extremity. IDO1 expression was determined using immunohistochemistry (IHC) performed on pretreatment pathology specimens. Two observers without knowledge of the clinic-pathological information evaluated the results of the IHC staining on the basis of a five-point scale: 0% for positive stainable cell number(-), 1-24% (1+), 25-49% (2+), 50-74% (3+), 75-100% (4+). The majority of cases (96%) showed positive immune-reactivity for IDO1 in malignant cells. The IDO1 level of expression was 22+ in 78% of cases. Patients with high IDO1 expression (4+, n=19) had a significantly lower metastasis free survival ($p=0.016$) and overall survival ($p=0.005$).[28] This data supports the hypothesis that immune tolerance mediated through IDO1 may have an important role in the tumorigenesis of osteosarcoma and other sarcomas and may exert a negative impact on clinical outcome and lends itself as a therapeutic target that warrants investigation in this group of tumors.

It is important to remember that IDO1 can be induced by IFNy and that IDO1 negative tumors may start expressing IDO1 when exposed to an inflammatory context such as that resulting from an immune response induced by anti-PD-1 or PD-L1 antibodies. In a Ewings sarcoma model, IDO1 was shown to be expressed in tumor cells as a consequence of IFNy produced by lymphocytes in response to IL2. In this preclinical study the impact of the cluster of differentiation 137 (CD137)/CD137 ligand (CD137L) on expression of IDO1 and other cytokines was analyzed in vivo and in vitro. Depending on the concentration of IL2, stimulation of CD137 produced a variation in expression of IDO1. At low IL2 concentrations IDO1 was reduced in the presence of the antibody against CD137. However, at high IL2 concentrations IDO1 was more highly expressed in the presence of CD137 antibodies. The cytokine analysis showed a correlation between IDO expression by tumor cells and IFNy secretion by peripheral blood mononuclear cells.[29] Hence, In IDO1 negative tumors, immunotherapies such as anti-PD1 and PD-L1 antibodies that stimulate the immune response may lead to the development of IDO1 expressing tumor cells that aim to suppress the immune response. In this setting, the addition of an IDO1 inhibitor could lead to an enhanced anti-tumor effect by blocking the immunosuppressive effects of IDO1. Tumor-induced IDO1 acts as a fundamental antagonist to anti-tumor immune responses generated by immunotherapy and may explain why only a minority of patients responds to checkpoint inhibition if administered as monotherapy.

Epacadostat

Overview

Epacadostat represents a novel, potent, and selective inhibitor of the enzyme IDO1. IDO1 mediates the catabolism of the essential amino acid tryptophan (Trp) to kynurenine (Kyn) within immune cells and a subset of tumor cells. This catabolism of Trp results in the inhibition of antitumor cell-mediated immune responses. Histologic evaluation of most human cancers shows extensive infiltration by inflammatory and immune cells, suggesting that the immune system does recognize and respond to the presence of the malignancy,[30] but in most cases the immune response is ineffective in inhibiting or eradicating tumor growth. Many tumor cells or the infiltrating immune cells overexpress IDO1, and there have been multiple lines of evidence to suggest that IDO1 is a key regulator in the immunosuppressive mechanisms responsible for tumor escape from immune surveillance.[31] Therefore, inhibition of this enzyme may provide a unique method to treat malignancies, either alone or in combination with chemotherapeutics or other immune-based therapies.

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

Clinical experience

As of 29 OCT 2016, 12 Incyte-sponsored clinical studies have either been completed or are ongoing (11 Phase 1 and 2 studies and 1 Phase 3 study). Three clinical studies have been completed (Studies INCB 24360-101, INCB 24360-102, and INCB 24360210). Seven ongoing studies (INCB 24360-201, INCB 24360-202, INCB 24360-203, INCB 24360-204, INCB 24360301, and INCB 24360-110, and INCB 39110-106) are combination therapy studies. Two ongoing studies (INCB 24360-103 and INCB 24360-104) are monotherapy studies. As of the cutoff date, 898 unique subjects have been exposed to INCB024360 in Incyte sponsored studies as monotherapy (149 subjects) and/or in combination with checkpoint inhibitors anti-programmed cell death protein-1 (PD-1) targeted therapy (543 subjects), anti-programmed death-ligand 1 (PD-L1) targeted therapy (124 subjects), anti-CTLA-4 targeted therapy (50 subjects), and a Janus kinase (JAK) inhibitor with JAK1 selectivity (32 subjects).

The safety profile of epacadostat monotherapy has been investigated in early phase clinical trials in the setting of advanced solid tumors. Epacadostat was generally well tolerated in subjects with refractory solid tumors at doses of up to 700 mg BID, and there appeared to be no correlation of dose with toxicity. Of the 52 subjects who were administered epacadostat, the median duration of treatment was 51.5 days. Eight subjects (15.4%) had an AE leading to death; of these 8 subjects, the cause of death was disease progression for 7 subjects and hypoxia for the remaining subject. Twenty-five subjects (48.1%) had an SAE during the study. Serious adverse events were observed in all 8 treatment groups. The most frequently reported SAE was disease progression (4 subjects, 7.7%), followed by abdominal pain, nausea, and hypoxia (3 subjects each, 5.8%). Treatment-emergent AEs were reported in all subjects. Fatigue was the most frequently

reported TEAE (36 subjects, 69.2%). The majority of subjects (90.4%) had treatment-related TEAEs. Fatigue and nausea were the most frequently reported treatment-related TEAEs (25 subjects each, 48.1%). The incidence and severity of fatigue were not dose related. Thirty subjects (57.7%) had TEAEs Grade 3 in severity and 7 subjects (13.5%) had a TEAE leading to discontinuation of study drug and withdrawal from the study. Two DLTs occurred; 1 DLT of radiation pneumonitis at the 300 mg BID dose level and 1 DLT of fatigue at the 400 mg BID dose level. A maximum tolerated dose was not determined. There were no clinically meaningful changes or trends noted in clinical hematology, chemistry, or urinalysis results or for vital signs, electrocardiograms, or physical examinations.

The safety profile of epcadostat in combination with pembrolizumab has been explored in a phase I study in the setting of patients with advanced melanoma and select solid tumors. This study included cohorts with escalating dose levels of epacadostat (25 mg BID (n = 4), 50 mg BID (n = 20), 100 mg BID (n = 18), and 300 mg BID (n = 18)) in combination with pembrolizumab 2 mg/kg or 200 mg IV administered every 3 weeks. A dose expansion portion of the study also enrolled patients to 4 dose levels of epacadostat (epacadostat 50, 100, and 300 mg BID) in combination with pembrolizumab 200mg IV every 3 weeks.

Enrollment to both study portions has completed. The preliminary safety results of this phase I study were presented at ESMO 2016 (these data have a cutoff of July 7th 2016). The maximum tolerated dose has not been established. Across all treatment groups, treatment-related AEs were reported in 50 subjects (81%). The most common (15%) all-grade treatment-related AEs (TRAEs) included fatigue (29%), rash (29%), arthralgia, pruritus, diarrhea, and nausea. Grade 3 TRAEs were observed in 18% of participants (rash [8%] and increased lipase [3%] were the most commonly experienced grade 3 treatment related adverse events). No treatment-related deaths occurred. A favorable objective response rate (58%), CR rate (26%), and a disease control rate (74%) among treatment-naive subjects with melanoma was observed. Responses were observed in all epacadostat dose cohorts 50 mg BID and all sites of target lesions including liver, lung, and lymph nodes. Objective responses were also observed in patients with previously treated advanced solid tumors other than melanoma.[51]

The safety profile for the 300mg bid dose of epacadostat in combination with pembrolizumab in the Phase 1/11 study 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. A phase III randomized, double-blind, placebo-controlled study of pembrolizumab in combination with epacadostat or placebo in subjects with unresectable or metastatic melanoma is underway. The dose of 100mg epacadostat in combination with pembrolizumab will be used in this study.

Other phase 1/11 studies examining epacadostat in combination with other checkpoint inhibitors such as nivolumab, atezolizumab and durvalumab are ongoing.

Pembrolizumab

Overview

Pembrolizumab is a highly selective humanized monoclonal lgG4-kappa isotype antibody against PD-1 currently approved by the *Food and Drug Administration* (FDA) for the treatment of patients with advanced melanoma at a dose of 2mg/kg given every 3 weeks.[32-35] Pembrolizumab has also received FDA approval for the treatment of patients with PD-L1 positive advanced non-small cell lung cancer[36] and patients with advanced head and neck squamous cell carcinoma.[37] Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on pembrolizumab.

Clinical Experience

The first dose-escalation phase 1 study involving patients with solid tumors showed that pembrolizumab was safe across 3 tested dose levels (1mk/kg; 3mg/kg and 10mg/kg) administered every 2 weeks; of note, the maximum tolerated dose was not reached and clinical responses were observed at all of the dose levels.[32] Subsequent studies confirmed the clinical activity of pembrolizumab. Hamid et al. initially investigated pembrolizumab at doses of 2mg/kg every 3 weeks and 10mg/kg given every 2 or 3 weeks in a melanoma-only cohort in a non-randomized fashion in the KEYNOTE-001 trial.[35] Objective responses occurred in 38% of 135 included patients. Grade 3 or 4 adverse events occurred in only 13% of the patients. In a subsequent cohort of the same KEYNOTE-001 phase I trial,[33]173 patients with advanced melanoma were randomized to receive pembrolizumab at 2mg/kg every 3 weeks or 10mg/mg every 3 weeks. ORR was 26% at both doses after a median follow up of 8 months, with no difference in OS between different doses (estimated OS at 1 year 58% vs 63%, 95% CI 0.68-1.75). In the expansion cohort of the same trial including a total of 411 patients, pembrolizumab resulted in objective responses in 40% of treatment naive patients. In the phase II study (KEYNOTE 002) patients with ipilimumab refractory advanced melanoma were randomized to receive pembrolizumab or investigator's choice of chemotherapy. A total of 540 patients were enrolled. Progression free survival was superior in the pembrolizumab arms compared to the chemotherapy arm. Efficacy was similar between pembrolizumab administered at a dose of 2mg/kg every 3 weeks versus 10mg/kg every 3 weeks and toxicity was less at the lower dose.[38] KEYNOTE-006 was a randomized phase Ill pivotal trial, designed to test whether pembrolizumab (10 mg/kg Q2W or 10 mg/kg Q3W) was superior to ipilimumab (IPI)(3 mg/kg Q3W) in the co-primary efficacy endpoints of progression-free survival (PFS) and OS in IPI-na'i've subjects with unresectable or metastatic melanoma. This trial demonstrated statistically significant improvements in OS and PFS for subjects randomized to pembrolizumab compared with subjects randomized to ipilimumab. The OS hazard ratio was 0.65 (95% CI: 0.52, 0.83) for the pembrolizumab arms combined over the IPI arm with a one-sided p-value of 0.0002.

The 12-month OS rate was 71.3% (95% CI: 67.3, 74.9) for the pembrolizumab arms combined. The HR PFS was 0.58 (95% CI: 0.46, 0.72) and 0.58 (95% CI: 0.47, 0.72) in the pembrolizumab 10 mg/kg Q2W arm and the pembrolizumab 10 mg/kg Q3W arm, respectively, versus the IPI arm, favoring the pembrolizumab arms.[34] Pembrolizumab treatment demonstrated superior efficacy compared to available treatment options (IPI, investigator's choice chemotherapy) in subjects with advanced melanoma who were treatment-na·1ve, as well as those who progressed on prior therapy, including IPI.

Two clinical trials were conducted to evaluate the efficacy of pembrolizumab in the treatment of NSCLC: KN001, KN010 KN024.

- KN001 was an open-label, Phase 1, first-in-human trial conducted to evaluate clinical activity of pembrolizumab as a single agent in solid relapsed/refractory malignancies, including NSCLC.

- KN010 was a randomized, adaptively designed Phase 2/3 trial of pembrolizumab at 2 dose levels versus docetaxel in subjects with NSCLC with PD-L1 positive tumors who had experienced disease progression after platinum-containing systemic therapy. Subjects were randomized according to their tumor proportion score (TPS) (extent of PD-L1 expression) defined as follows: a TPS 50% was considered strongly positive and a TPS = 1% to 49% was considered weakly positive.[39]

In the KN-001 trial the overall response rate by RECIST 1.1 among all subjects treated was 42.6%. For the KN010 Intent-to-treat (ITT) Population (TPS 50%), the HR for OS was 0.54(95% CI: 0.38, 0.77) with a one-sided p-value of 0.00024 in the pembrolizumab 2 mg/kg Q3W arm vs. the docetaxel arm. The HR for OS was 0.50 (95% CI: 0.36, 0.70) with a one-sided p-value of 0.00002 in the pembrolizumab 10 mg/kg Q3W arm vs. the docetaxel arm. The median OS was 14.9 months in the 2 mg/kg Q3W arm and 17.3 months in the 10 mg/kg Q3W arm compared with 8.2 months in the docetaxel arm. For the KN010 ITT population with TPS 1 %, the OS HR for pembrolizumab 2 mg/kg versus docetaxel was 0.71 (95% CI: 0.58, 0.88), with a p-value of 0.00076. The OS HR for pembrolizumab 10 mg/kg vs docetaxel was 0.61 (95% CI: 0.49, 0.75), with a p-value <0.00001.[39]

Overall, the results from KN001 and KN010 demonstrated that pembrolizumab provided substantial, clinically meaningful benefits in OS, PFS, and ORR in subjects with NSCLC who progressed after platinum-containing chemotherapy and whose tumor cells expressed PD-L1. The PD-L1 selection employed in KN010 identified patients more likely to benefit from pembrolizumab and resulted in favorable HRs in OS compared with docetaxel. In previously treated subjects with NSCLC with PD-L1 TPS 1 % and disease progression following platinum-containing chemotherapy, pembrolizumab provides a statistically

significant and clinically meaningful OS benefit compared with standard docetaxel chemotherapy. Pembrolizumab was subsequently explored in a randomized, phase III study examining pembrolizumab compared to platinum-based chemotherapy in patients with treatment-na·1ve, advanced, NSCLC with PO-L1 expression on at least 50% of tumor cells without evidence of sensitizing EGFR mutation or ALK gene fusion. Pembrolizumab was shown to produce a significantly longer PFS, OS and improve response rates compared to chemotherapy (Keynote-024).[36]

KEYNOTE_012 trial was a non-randomized trial exploring the safety and anti-tumor activity of pembrolizumab monotherapy in patients with advanced solid tumors including head and neck, triple negative breast cancer, gastric cancer and urothelial cancer. This trial enrolled 192 patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC). Robust anti-tumor activity was demonstrated in this cancer subtype with an objective response rate of 21.9% in HPV+ve patients and 15.9% in HPV -ve patients. The median overall survival was 8.5 months and the 6-month progression free survival rate was 24.9%.[40] Pembrolizumab has a positive benefit-risk profile and is well tolerated in the approved indications, as evidenced by a low rate of toxicity Grade 3 to 5 drug-related AEs (13.8%), discontinuations due to AEs (11.9%), and deaths due to drug-related AEs (0.4%). Furthermore, the frequency of immune-mediated AEOSIs is low, and these events are readily managed in the clinical setting. The safety and efficacy data generated to date provide a favorable benefit-risk assessment for the use of pembrolizumab as a treatment for subjects with advanced/metastatic melanoma, NSCLC, and HNSCC

Identifying predictive biomarkers to immunotherapy

One major challenge to harnessing immune checkpoint inhibitors in sarcomas is identifying patients who have the highest chance of benefiting from this modality of therapy. To address this question, lessons can be extrapolated from other tumor types and applied to sarcomas. We believe the heterogeneity inherent to sarcomas makes them an ideal group of tumors to validate a prospective biomarker for response to immune activating agents.

It is unclear how best to predict which patients will benefit from immune checkpoint inhibitors. Expression of PO-L1 on tumor cells can predict benefit to anti-PO-1 therapy however; PO-L1 negativity does not preclude durable responses to anti-PO-1 agents in patients with melanoma. In the Keynote-006 study that explored the role of pembrolizumab in patients with advanced, ipilimumab-na"i"ve, melanoma, 80% of the patients had tumors that were PO-L1 positive, 18% were PO-L1 negative and PO-L1 status was unknown in 2%. Progression free survival (PFS) and objective response rate (ORR) were improved with pembrolizumab irrespective of the PO-L1 status. However, overall survival was improved only in PO-L1 positive patients. The disproportionate representation of PO-L1 positive versus negative patients in this study should be considered when interpreting this result.[41]

In the Keynote-001 study Daud et al, has explored the relationship between anti-PD-1 activity and PD-L1 expression in patients with advanced melanoma. The ORR was highest in the PD-L1 strong group (41.0%) compared to other treatment groups.[42]

In the case of non-small cell lung cancer, data from Keynote-001 and Keynote-010 studies indicated that patients with a PD-L1 tumor proportion score of 50% or greater were more likely than those with lower tumor proportion scores to respond to pembrolizumab. Similarly, in Keynote-024, patients with advanced, treatment-na"i"ve, NSCLC with PD-L1 tumor proportion score of 50% had longer PFS and OS than patients randomized to and treated with platinum-based chemotherapy.[36] Pembrolizumab obtained FDA approval for the treatment of advanced, treatment refractory, PD-L1 positive, NSCLC, in association with a companion diagnostic tool, the PO-L1 IHC 22C3 pharmOx test, the first test designed to detect PO-L1 expression in non-small cell lung tumors.

It is known that PO-L1 expression remains a dynamic marker that can change over time and under different conditions in the microenvironment. Tumor heterogeneity can also contribute to varied PO-L1 expression.[43] These data suggest that PO-L1 expression may change as a result of therapy with immune checkpoint inhibitors or that other mechanisms underlie the response to immune checkpoint blockade. There remains the need to further define the role of PO-L1 as a biomarker predictive of response to PO-1 blockade in all tumor types in which it is investigated.

Tumor Neoantigens May Underlie Response to Immune Checkpoint Inhibition

Van Rooij et al associated a response to ipilimumab in a patient with melanoma with T cell recognition of a tumor-specific mutant protein, termed a 'neoantigen' .[44] To do this, they performed whole exome sequencing of the melanoma tumor tissue and tumor infiltrating lymphocytes (TILs) and identified >1000 tumor-specific mutations. They then utilized NetMHC, an online predictor of Class I major histocompatibility complex (MHC)-specific affinities for specific sequences of 9-11 amino acids, to narrow the mutant sequences to 448 peptides predicted to bind with medium to high affinity to the patient's COB+ T cells.[45] These peptides were screened for binding with patient TIls, and they identified 3.3% of all patient COB+ T cells reacted with a specific mutated epitope in the ataxia-telangiectasia and Rad3-related protein (ATR) pathway, suggesting this resulted in the clinical benefit seen in this patient.

Further support for neoantigen-specific immune surveillance has come from in vivo models of sarcoma. In a murine model of chemically-induced sarcomas arising in immune-deficient *Rag2-*^{1}- mice, Matsushita et al reported that implantation into an immunocompetent murine host resulted in "immune editing" of the tumor, and tumors with a greater neoantigen load were frequently rejected by the new host.[46] Similar results were seen in a conditional Kras-p53 knockout mouse model. Whereas the work of van Rooij et al and Matsushita et al

suggests that certain key mutations predict response, DuPage et al and other authors imply that a higher overall mutational load and resulting neoantigen burden may lead to efficacy.[47]

The Chan lab at MSKCC has proprietary data supporting the association between this patient-specific neoantigen analysis in melanoma with individual clinical benefit from ipilimumab and tremelimumab. Whole exome sequencing was performed on tumor tissue and matched blood samples from 64 patients with melanoma who were treated with anti-CTLA-4 blockade (ipilimumab or tremelimumab). A neoantigen signature incorporating both mutational load and patient-specific neoantigens was shown to separate patients with prolonged clinical benefit from patients with progressive disease. They then validated this signature in another set of 39 patients with melanoma who were treated with anti-CTLA-4 antibodies. In this validation set predicted neoantigens activated T cells from patients treated with ipilimumab. This work defines a genetic basis for benefit to anti-CTLA-4 blockade in melanoma and provides strong rationale for examining exomes of patients receiving other immunotherapies to similarly see if a genetic basis can be defined for response or resistance to these immunotherapies.[48]

Sarcoma is an ideal tumor subtype in which to test this hypothesis prospectively. The Singer laboratory at MSKCC has shown that different histologies show markedly different amounts of genetic alteration.[86] It is perhaps not surprising that a previous pilot study of ipilimumab in synovial sarcomas, a translocation-positive, genetically "simpler" tumor, produced no clinical responses.[49] There are currently no published whole exome mutation studies in sarcoma, which underscores how important this research will be to the sarcoma community.

Summary Statement

MSKCC is a leading sarcoma research center with the expertise, resources, and high clinical volume to conduct scientifically sound clinical studies. Sarcoma is an immunogenic malignancy with a need for more therapeutic options. Prior immunotherapeutic agents have shown promise in select sarcoma patients. Using a combination of epacadostat, an IDO inhibitor, and the anti-PD1 monoclonal antibody, pembrolizumab, to treat patients with sarcomas and our planned scientific correlates, we believe we can assess the safety and efficacy of dual checkpoint inhibition and better understand the effects of combined immunotherapy in antitumoral immune response. The safety of this combination therapy has been explored in a phase I study in the setting of patients with advanced (checkpoint inhibitor na·1ve) melanoma and select solid tumors. The combination therapy was safe and well tolerated. The recommended phase II dose of epacadostat was identified as 100mg bid in combination with pembrolizumab delivered at a dose of 200mg intravenously on a three weekly basis. The combination also showed promising clinical activity.[50] Consequently, enrollment in tumor-specific cohorts is ongoing in phase 2 of this study and a phase 3 study in patients who are treatment-naive for advanced melanoma has been initiated (NCT0275207 4).

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is a single-center, phase II study to evaluate the efficacy of the 1001 inhibitor, epacadostat, given in combination with the anti-PD1 monoclonal antibody, pembrolizumab, for patients with metastatic and/or locally advanced grade sarcomas.

A total of 30 patients will be enrolled onto the study. Patients will be enrolled onto one of 4 cohorts. Each cohort will enrol a prespecified number of patients with certain sarcoma histological subtype(s). The 4 patient cohorts and the number of patients eligible to enrol per cohort in this study are as follows:

A) Undifferentiated Pleomorphic Sarcoma (UPS), Liposarcoma (dedifferentiated or pleomorphic liposarcoma), or Myxofibrosarcoma (n=10)

B) Leiomyosarcoma (n=5)

C) Vascular Sarcoma Subtypes (including angiosarcomaEpithelioid Hemangioendothelioma (EHE))) (n= 5)

D) Other (n=10)

This study will be conducted using a one-stage design. Patients will receive the recommended phase II dose (100mg bid) of epacadostat, when administered in combination with pembrolizumab. Epacadostat 100mg will be administered orally, twice daily, continuously for 21 days. Pembrolizumab will be administered at a dose of 200mg every 21 days (±3 days). Treatment with epacadostat and pembrolizumab will start on day 1 of the first cycle. Each cycle will consist of 21 days.

Patients will be evaluated radiographically at baseline, week 8 (+/- 7 days) and every 8 weeks(+/- 7 days) subsequently until week 56 and then every 12 weeks thereafter or as per the discretion of the treating investigator. Response will be assessed using RECIST v1.1 (primary response assessment) and immune-related response evaluation criteria of solid tumors (irRECIST) (secondary response assessment).

All study participants where feasible will undergo mandatory tumor biopsies at baseline and week 7. Optional biopsies at progression will be offered. Biopsies must be collected within +/- 7 days of the originally scheduled timepoint.Serial blood samples will be obtained at baseline, during, and at the end of study treatment.

Study therapy should continue once there is no evidence of progression of disease per RECIST 1.1, no clear clinical deterioration and the patient is able to tolerate the treatment. Treatment beyond progression will be allowed at the discretion of the clinical investigator

as long as patient is clinically benefitting, is tolerating the drug well and continues to meet all study treatment criteria.
The safety of the combination of epacadostat and pembrolizumab in patients with advanced sarcoma will be determined using CTCAE v4.03 criteria for toxicity assessment. Safety data will be collected for up to 90 days following the last dose of the study drugs. Therapy will be discontinued due to confirmed progression of disease or clinical progression, intercurrent illness that prevents further administration of treatment or intolerance of study treatment. Study personnel will attempt to collect survival status for all patients after the end-of-study visit every 3 months via telephone, email, or another method for up to 1 year.

4.2 Intervention

Patients will start both study drugs on day one of the first and subsequent treatment cycles. One treatment cycle consists of 21 days.

100mg tablets of epacadostat will be administered orally, twice daily continuously for 21 days (Table 1).

Pembrolizumab will be administered at a dose of 200mg every 21 days (±3 days). Pembrolizumab infusion should be administered in 30 minutes, with a window of -5 and +10 minutes, using an infusion pump.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 Epacadostat (formerly known as INCB024360)

5.1.1 Mechanism of Action of Epacadostat

Epacadostat represents a novel, potent, and selective inhibitor of the enzyme IDO1. IDO1 catabolism of Trp inhibits T-cell-mediated immune responses. IDO1 expression has been shown to be elevated in many human cancers, including sarcomas. IDO1 inhibition may restore an effective antitumor immune response and may provide a method to treat malignant diseases either alone or in combination with chemotherapeutics and/or immunotherapy-based strategies. In cell-based assays, epacadostat potently inhibits IDO1 in both human tumor cells and human dendritic cells (DCs) resulting in reduced Trp to Kyn conversion (IC50 values= 7.1-12.7 nM). Epacadostat does not significantly inhibit other proteins that could impact Trp catabolism.

5.1.2 Formulation, Storage and Packaging

Epacadostat will be supplied as an immediate release tablet in two strengths (25 mg, 100 mg) for oral use. The tablets contain the active drug (epacadostat) along with commonly used compendia! excipients (lactose monohydrate, microcrystalline cellulose, povidone, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate).

Once received by a designated staff member at the study site, epacadostat must be handled and stored safely and properly and kept in a secured location to which only the investigator and designated assistants have access to. Upon receipt, epacadostat should be stored according to the instructions specified on the drug labels. In general epacadostat tablets should be stored at ambient conditions (15°C-30°C or 59°F-86°F).

5.1.3 Administration of Epacadostat

Epacadostat be taken orally twice daily on a continuous dosing schedule at the recommended phase II dose for epacadostat when administered in combination with pembrolizumab. Epacadostat will be administered as a flat-fixed dose, and not by body weight or body surface area. Patients will be provided with a 3 week supply of epacadostat for self-administration at home until at least their next scheduled study visit. Patients will be instructed to return unused study drug to the site at each visit. A study medication diary will be completed by the patients for each dose of epacadostat.

Epacadostat will be taken twice daily orally without regard to food morning and evening, approximately 12 hours apart. There is no priority to the order of administration of epacadostat and pembrolizumab when given in combination; however, th dose of epacadostat should be taken as close to the regularly scheduled 12-hour dosing interval as possible. Patients will be instructed not to chew or crush tablets of study drug. If a patient vomits at any time after dosing, the dose of study drug should not be re-administered. Doses of study drug omitted for AEs or any other reason should not be made up later in the day, or at the end of the dosing period. If a dose of epacadostat is missed, the subject should take it as soon as possible within 4 hours of the missed dose. If 4 hours passes, the subject should skip the missed dose and take the next dose as scheduled. All missed doses and schedule deviations should be recorded in the pill diary. Doses of epacadostat will be self-administered except on the days scheduled to be given at the time of a study visit.

5.2 Pembrolizumab

5.2.1 Mechanism of Action of Pembrolizumab

Pembrolizumab (formerly known as MK-3475 or lambrolizumab), is a highly selective humanized monoclonal IgG4-kappa isotype antibody against PD-1, that acts by blocking its interaction with PD-L1 and PD-L2. Pembrolizumab is currently approved by the FDA for the treatment of patients with unresectable or metastatic melanoma as i) initial first-line therapy[34] and ii) following disease progression on ipilimumab and/or , if BRAF V600 mutation positive, a BRAF inhibitor.[33,38] Pembrolizumab is also approved by the FDA for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 as determined by an FDA-approved test in the first-line setting or with disease progression on or after platinum-containing chemotherapy. Patients with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic

tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving pembrolizumab. Pembrolizumab is approved for use with a companion diagnostic, the PD-L1 IHC 22C3 pharmDx test, the first test designed to detect PD-L1 expression in NSCLC tumors.[36] The FDA approved pembrolizumab for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy.[37]

Pembrolizumab is currently being explored both as monotherapy and in combination with other therapies across more than 30 tumor types. The combination of pembrolizumab and epacadostat has been investigated in a phase I study including patients with advanced melanoma or other select solid tumors. The combination was safe, well tolerated and showed promising clinical activity in melanoma and other tumor types. Based on this data enrollment in tumor-specific cohorts is ongoing in phase 2 of this study and a phase 3 study in treatment na·1ve patients with advanced melanoma has been initiated.[51]

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T cell proliferation and cytokine production. Upregulation of PD-1 ligands occur in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.

The theoretical molecular weights of the heavy and light chains derived from the amino acid sequences, excluding glycosylation, are 49.4 kDa and 23.7 kDa, respectively. The antibody is heterogeneously glycosylated at asparagine 297 within the Fe domain of each heavy chain, yielding molecular weights typically ranging between 148.9 and 149.5 kDa, depending on the attached glycan chains.

5.2.2 Formulation, Storage and Packaging of Pembrolizumab

Pembrolizumab will be manufactured by Merck.

Pembrolizumab is supplied as pembrolizumab 50 mg lyophilized powder in a single-use vial for reconstitution or as Pembrolizumab 100 mg/4ml Solution for Injection

Reconstituted and diluted solutions of pembrolizumab should be stored either:

- At room temperature for no more than 4 hours from the time of reconstitution. This includes room temperature storage of reconstituted vials, storage of the infusion solution in the IV bag, and the duration of infusion.

- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of reconstitution. If refrigerated, allow the diluted solution to come to room temperature prior to administration.

Product should not be frozen.

5.2.3 Administration of Pembrolizumab

Pembrolizumab must be prepared and administered by a qualified healthcare professional.

Pembrolizumab at a dose of 200 mg will be administered intravenously on Week 1 of treatment cycle 1 and every 3 weeks (±3 days) thereafter.

Pembrolizumab infusion will be administered as a 30-minute intravenous infusion. Investigators should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+ 10 min). A central catheter is not required for infusion; however if a subject has a central venous catheter in place, it is recommended that it be used for the infusion. A 0.2 or 0.22 µm in-line filter made of polyethersulfone (PES) must be used during administration to remove any adventitious particles. If the infusion set does not contain a 0.2 or 0.22 µm in-line filter, it is recommended to use an extension line containing the filter.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

Patients must fulfill all of the following criteria to be eligible for admission to the study:

- Male or female age 18 years at the time of informed consent
- Be willing and able to provide written informed consent/assent for the trial
- Be willing to comply with treatment protocol
- Subjects must have a histologically confirmed metastatic and/or locally advanced sarcoma
- Adequate performance status: ECOG O or 1/KPS 100-70%
- Subjects must have at least one prior line of systemic therapy (e.g. chemotherapy, immunotherapy, targeted or biological therapy) for their sarcoma. An exception to this criterion will be made for patients with sarcoma histological subtypes for which there is

no known standard systemic therapy (e.g., chondrosarcoma). Any patient that refuses standard chemotherapy for the treatment of their disease is also considered eligible. Prior adjuvant therapy will not count provided it was completed more than 6 months previously.

- Presence of measureable disease per RECIST v1.1.Target lesions must not be chosen from a previously irradiated field unless there has been radiographically and/or pathologically documented tumor progression in that lesion prior to enrollment.
- All subjects must agree to pre-treatment tumor biopsy. 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.

- Adequate organ function determined within 21 days of treatment initiation, defined as per Table 2:

Table 2: Definition of Adequate Organ Function

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	1,000 Imel
Platelets	75,000 / mcl
Hemoglobin	I B g/dl or 5.0 mmol/L
Renal	
Serum creatinine **OR** Measured or calculated[8] creatinine clearance (GFR can also be used in place of creatinine or CrCI)	S1.5 X upper limit of normal (ULN) **OR** 60 ml/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	1.5 X ULN **OR**
	Direct bilirubin s ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	s 2.5 X ULN **OR** **s** 5 X ULN for subjects with liver metastases
Albumin	2.5 mg/dl
Coagulation	
International Normalized Ratio [52] or Prothrombin Time [53]	s1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	s1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

acreatinine clearance should be calculated per institutional standard.

- Women of childbearing potential must have a negative serum pregnancy test at screening and :5 72 hours prior to day 1 of study treatment.

- Male and female subjects of childbearing potential must be willing to use an adequate method of contraception as outlined in Section 11.7, for the course of the study through 120 days after the last dose of study medication.

  Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

6.2 Subject Exclusion Criteria

Patients who fulfil any of the following criteria are not eligible for admission to the study:

- Uncontrolled intercurrent illness including current active infection requiring systemic therapy or symptomatic congestive heart failure within 6 months
- Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

- Evidence of clinically significant immunosuppression such as the following:

  Primary immunodeficiency state such as Severe Combined Immunodeficiency Disease

  - Concurrent opportunistic infection

  Receiving systemic immunosuppressive therapy(> 2 weeks) including oral steroid doses > 10 mg/day of prednisone or equivalent within 7 days prior to enrollment. However, in the setting of non-immune mediated indications for steroid use, chronic/active low dose steroid use may be permitted at the discretion of the principal investigator. The dose of steroid allowed in this setting is also at the discretion of the principal investigator. (Use of inhaled or topical steroids is permitted.)

- History or evidence of symptomatic autoimmune disease (e.g., pneumonitis, glomerulonephritis, vasculitis, or other), or history of active autoimmune disease that has required systemic treatment (i.e., use of corticosteroids, immunosuppressive drugs or biological agents used for treatment of autoimmune diseases) in past 2 years prior to enrollment. Replacement therapy (e.g., thyroxine for hypothyroidism, insulin for diabetes or physiologic corticosteroid replacement

therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment for autoimmune disease.

- Known history of human immunodeficiency virus (HIV) (HIV 1/2 antibodies) disease
- Has known active Hepatitis B (e.g., Hepatitis B Virus PCR is detected) or Hepatitis C (e.g., HGV RNA [qualitative] is detected).

- Patients who have received a live vaccine within 30 days of the start date of the planned study therapy. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, Bacillus Calmette-Guerin (BCG), and typhoid vaccine. Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.
- Has a known history of active TB (Bacillus Tuberculosis)
- Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 2 weeks of the first dose of treatment.

- Has had a prior chemotherapy, immunotherapy, biological therapy, targeted small molecule therapy, or radiation therapy within 3 weeks prior to study Day 1 or who has not recovered (i.e., $ Grade 1 or at baseline) from adverse events due to previously administered agent.
    - Note: Subjects with$ Grade 2 neuropathy, alopecia or hypothyroidism are an exception to this criterion and may qualify for the study.
    - Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy events due to a previously administered agent.
- Presence of a gastrointestinal condition that may affect drug absorption
- Known allergy or reaction to any component of either study drug formulation
- Women who are pregnant or breast feeding
- Subjects expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of study treatment(s).
- Inability to comply with protocol required procedures

- Subjects receiving Monoamine Oxidase Inhibitors (MAOIs) or drug which has significant MAOI activity (meperidine, linezolid, methylene blue) within the 21 days before screening.
- Any history of Serotonin Syndrome (SS) after receiving serotonergic drugs.
- History or presence of an abnormal electrocardiogram (ECG) that, in the investigator's opinion, is clinically meaningful. Screening QTc interval *z* 480 milliseconds is excluded. In the event that a single QTc is *z* 480 milliseconds, the subject may enroll if the average QTc for the 3 ECGs is< 480 milliseconds. For subjects with an intraventricular conduction delay (QRS interval > 120 milliseconds), the JTc interval may be used in place of the QTc with the approval of the principal investigator. The JTc must be < 340 milliseconds if JTc is used in place of the QTc. Subjects with left bundle branch block are excluded.

  Note: QTc prolongation due to pacemaker may enroll if the JTc is normal.
- Use of any UGT1A9 inhibitor from screening through follow-up period, including the following: diclofenac, imipramine, ketoconazole, mefenamic acid, and probenecid.
- History of prior therapy with an IDO1 inhibitor in combination with an anti-PD-1/anti-PD-L1 agenUany other drug specifically targeting checkpoint pathways. Patients who have received prior therapy with single agent anti-PD-1/anti-PD-L1 therapy or single agent IDO1 inhibitor will be eligible for this study.
- Presence of any other concurrent active malignancy

7.0 RECRUITMENT PLAN

Both men and women and members of all races and ethnic groups are eligible for this trial. The clinical trial will be listed on the clinicaltrials.gov website and on the websites of participating institutions. Patients will be identified through internal referrals and external referrals by Medical and Surgical Oncologists, nationally and internationally. Patients will be recruited through the Sarcoma Disease Management Team of the Memorial Sloan Kettering Cancer Center. The Sarcoma Service and the Sarcoma Disease Management Tearn each hold weekly interdepartmental meetings to identify study participants for open clinical trials. We will also discuss the trial and patient recruitment with several Sarcoma patient support groups. The principal investigator will be available to all patients for further questions and information through a contact number, which will be provided on the consent form.

8.0 PRETREATMENT EVALUATION

Screening

All aspects of the screening evaluation should be completed prior to entering the study, unless otherwise noted. Pretreatment evaluations include:

Informed consent

Confirmation of disease: documented presence of metastatic and/or locally advanced sarcoma with RECIST v1.1 measureable disease.
Pathologic confirmation of the presence of a sarcoma at the study site
All patients enrolled in this study will undergo a new baseline biopsy where feasible
Full medical history, physical exam, assessment of performance status by KPS or ECOG status
Review of concomitant medications
Complete vital signs (pulse, blood pressure, temperature, respiratory rate, oxygen saturation) as well as weight and height. Height may be documented at any time prior to registration.
Standard baseline imaging of chest, abdomen, pelvis (CT or MRI), with CT scan or MRI of brain or other site if applicable.
12-lead electrocardiogram (ECG)
Echocardiogram (ECHO)
Serum pregnancy test for women with child-bearing potential.
Complete blood count with differential.
PT (or **INR)** and aPTT
Comprehensive metabolic panel (glucose, blood urea nitrogen, creatinine, sodium, potassium, chloride, bicarbonate, calcium, total protein, albumin, serum bilirubin, alkaline phosphatase, ASL, AST), phosphorus, magnesium,
TSH, T4 free, T3
Amylase, lipase.
Review of inclusion and exclusion criteria

Baseline assessments including biopsy must be done within 3 weeks of starting protocol therapy. Note, previous pathologic confirmation of the presence of sarcoma at the study site prior to within 3 weeks of starting protocol therapy allowed.

Please refer to Study Calendar in Section 10 for additional information.

9.0 TREATMENT/INTERVENTION PLAN

9.1 Study drugs

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in section 11.0. Modifications and dose delays due to toxicity are described further in section 11.4. The schedule of evaluations and interventions is described in Section 10.

Patients will be treated with epacadostat (100mg tablet), administered orally in tablet form, twice daily, continuously for the 21 days of each treatment cycle, beginning on day 1. Pembrolizumab 200mg/dose will be administered by intravenous infusion on day 1 of cycle one and every three weeks thereafter (±3 days). Pembrolizumab infusion should be administered in 30 minutes, with a window of -5 and +10 minutes, using an infusion pump.

The treatment period with the combination therapy or pembrolizumab will continue every 21days for up to 35 cycles (approximately 2 years) as long as subjects are receiving benefit from treatment and have not had disease progression or met any criteria for study withdrawal and are tolerating therapy. In the case of a patient benefiting from study therapy who discontinue study treatment after the maximal therapy duration of 2 years and subsequently experience disease progression, re-challenge with study therapy will be permitted.

No additional investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy

9.2 Dose rationale

The dose combination of 100mg bid epacadostat plus pembrolizumab for the ongoing phase III melanoma study is based upon a benefit/risk assessment made specifically in melanoma in collaboration with Merck. In the phase 1/11 study examining this combination, there was evidence of improved efficacy in melanoma subjects at all doses of epacadostat from 50 to 300mg bid. The same dose of the combination therapy of epacadostat and pembrolizumab will be use in this phase II study as is being used in the melanoma specific phase III study.

9.3 Duration of Therapy

Study treatment may continue until one of the following criteria applies:

Until a total of 35 cycles (approximately 2 years) of treatment has been administered as long as subjects are receiving benefit from treatment and have not had disease progression or met any criteria for study withdrawal outlined below

Clinical or radiographic disease progression as defined by RECIST 1.1. Patient may be allowed to continue treatment after progression if they are deriving clinical benefit (section 9.4).

Intercurrent illness that prevents further administration of treatment

Intolerance of study treatment

Patient decides to withdraw from the study

Physician decides to withdraw a patient from the study for a reason not listed here

Pregnancy in patient

The patient is lost to follow-up

Inability of the patient to comply with the requirement of the protocol for treatment or evaluation.

End of study, whichever occurs first.

9.4 Treatment Beyond Initial RECIST 1.1 Defined Progression of Disease

Due to the mechanism of action, subjects may experience growth in existing tumors or the appearance of new tumors prior to maximal clinical benefit of the combination therapy of epacadostat and pembrolizumab. The patient may be allowed to continue study treatment after initial RECIST 1.1 defined progression if they are assessed by the treating physician to be deriving clinical benefit and tolerating study treatment. The treating physician may consult with the overall study PI for help with assessing the patient. Patients who decide to continue study therapy on protocol after initial radiolgic evidence of disease progression will need to provide written informed consent at the time of the decision to treat beyond initial evidence of progression of disease on study therapy. Such patients should discontinue study therapy upon further evidence of progression at the discretion of the treating physician.

9.5 General Concomitant Medication and Supportive Care Guidelines

Supportive Care: Best supportive care and treatment will be given as appropriate to each subject as per Clinical Center and ASCO guidelines (antiemetics, antibiotics, packed red blood cell and platelet transfusions, nutritional support, non-radiation palliative treatment for pain).

Steroids: Doses up to 10mg of prednisone daily (or equivalent) will be allowed concurrently with continuous treatment with epacadostat and/or pembrolizumab.

If the subject requires corticosteroid dosing of >10 mg prednisone daily (or equivalent) and/or other immunosuppressive medication for related toxicities, epacadostat and pembrolizumab dosing must be held until the corticosteroid dose has decreased to 10 mg prednisone daily (or equivalent) and the administration of the other

immunosuppressive medication has discontinued. Higher doses of prednisone (.i.e., >10mg) may potentially be allowed in combination with the study therapy if they are prescribed for non-immune mediated indications at the discretion of the principal investigator.

Radiation: Radiation therapy are only allowed during the study if required for palliation of symptoms due to underlying sarcoma.

Non-Surgical

Local Interventions: Non-surgical local interventions are only allowed during the study if required for palliative of symptoms due to underlying sarcoma

Surgery: Subjects must not schedule any elective surgeries during the treatment period and for at least 30 days after the last administration of study drugs. If a subject undergoes any unexpected surgery or local intervention during the course of the study, all study treatments must be withheld and the investigator or designee should notify the sponsor' as soon as possible. A subject may be allowed to resume study drugs if both the investigator and sponsor's medical monitor agree to restart study therapy

Other supportive measures and specific treatments/guidelines recommended for the management of toxicities are detailed in Appendix B.

9.6 Drug Interactions

9.6.1 Epacadostat

9.6.1.1 Restricted Medications/Treatment

- Systemic steroids may be used at doses 10 mg/day prednisone or equivalents. However, in the setting of non-immune mediated indications for use, chronic/active low dose steroid use at doses >10mg/day prednisone or equivalents, may be permitted at the discretion of the principal investigator.

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 100 mg BID, the dose of

warfarin should be maintained and close INR monitoring is recommended. Based on PK/PD modeling, recommendations for warfarin dose modifications for subjects receiving epacadostat :s; 100 mg BID are summarized in Table 3 below based on the INR prior to starting epacadostat.

Table 3. Recommendations for Warfarin dose modification in setting of concomitant epacadostat

Stable Baseline INR	Epacadostat Dose :S 100 mg BID
INR :::;2.5	Close INR monitoring
INR > 2.5	Close INR monitoring

- 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.

9.6.1.2 Prohibited Medications/Treatment

Subjects are prohibited from receiving the following therapies starting from screening through end of treatment phase of this study unless otherwise noted below:

- Any investigational medication other than the study drugs.
- Use of any anticancer medications, including chemotherapy or biologic therapy other than the study medications.
- Any chronic immunological-suppressive treatment. **(Note:** Inhaled or topical steroids are allowed, and systemic steroids at doses :510 mg/day prednisone or equivalents are allowed and immune suppressants are allowed for short-term treatment for immune toxicities or as prophylaxis for contrast allergy for imaging procedures. Steroid use at doses >10mg/day prednisone or equivalents for non-immune mediated indications may be permitted at the discretion of the principal investigator)
- Radiation therapy

  Note: In the presence of a mixed response (some lesions improving or stable and other lesions progressing), radiation therapy to a symptomatic solitary lesion or to the brain is allowed.
- Administration of a live attenuated vaccine within 30 days before the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed;

however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

- Use of any MAOI or drug associated with significant MAOI activity agents is prohibited from 21 days prior to Day 1 through 2 weeks after the final dose of epacadostat has been administered
- Use of any immunological-based treatment for any reason from screening through follow-up visit is prohibited.

  Note: Completed adjuvant therapy (eg, vaccines) with medical monitor approval, inhaled or topical steroids, and systemic steroids at doses 10 mg/day prednisone equivalents are allowed, as described in Restricted Medications.
- Any UGT1A9 inhibitor, including acitretin, amitriptyline, androsterone, cyclosporine, dasatinib, diclofenac, diflunisal, efavirenz, erlotinib, estradiol (17-beta), flutamide, gefitinib, gemfibrozil, glycyrrhetinic acid glycyrrhizin, imatinib, imipramine, ketoconazole, linoleic acid supplements, mefenamic acid, mycophenolic acid, niflumic acid, nilotinib, phenobarbital, phenylbutazone, phenytoin, probenecid propofol, quinidine, ritonavir, sorafenib, sulfinpyrazone, valproic acid, and verapamil.

Subjects 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.

9.6.2 Pembrolizumab

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

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

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy
    - Note: Radiation therapy to a symptomatic lesion or to the brain may be allowed at the investigator's discretion.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses or higher of corticosteroids for non-immune mediated indications may be approved after consultation with the principal investigator.

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

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

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

10.0 EVALUATION DURING TREATMENT/INTERVENTION

10.1 - Pre-treatment diagnosis confirmation

All patients will have histological confirmation of their diagnosis prior to treatment. Baseline clinical and radiologic evaluations are to be conducted within 3 weeks of starting protocol therapy. In addition, a mandatory baseline biopsy will be performed within 3 weeks of first dose of the study drugs for all patients enrolled in the study where feasible.

10.2 - Standard evaluations

Evaluations at clinic visits will occur on day 1 (± 3 days) of cycle 1 and every cycle thereafter. The clinical evaluations are delineated further in the study calendar (Table 5) and include:

- Full medical history, physical exam, assessment of performance status by KPS or ECOG status
- Review of concomitant medications

  Complete vital signs (pulse, blood pressure, temperature, respiratory rate, and oxygen saturation) as well as weight and height. Height may be documented at any time prior to registration.

All patients will undergo a baseline staging CT scan of the chest (with or without contrast), abdomen and pelvis (with or without contrast), and MRI of the affected area if deemed necessary by the treating physician. Response evaluations will occur at week 8 and every 8 weeks subsequently (± 1 week window) until 56 weeks, and then every 12 weeks thereafter or as per the discretion of the treating investigator.

Routine/standard blood samples will be obtained at screening, day 1 of cycle 1 and then prior to every scheduled treatment visit (± 3 days) thereafter. All routine blood samples should be obtained prior to the daily dose epacadostat and/or pembrolizumab. These samples will be used for routine tests and are part of standard of care. The following analyses will be assessed at various time points during the study:

Hematology: Complete blood count with differential
Chemistry: phosphorus, magnesium
Serum pregnancy test for women with child-bearing potential
Comprehensive metabolic panel (sodium, potassium, chloride, bicarbonate, calcium, glucose, blood urea nitrogen, creatinine, total protein, albumin, serum bilirubin, alkaline phosphatase, ASL, AST)
TSH, T4 free, T3
Amylase and lipase
Additional tests if clinically indicated

10.3 Required Laboratory Parameters for Treatment

A new dose of therapy may be initiated provided that the patient meets the following criteria on the day of treatment:

- ANC 1,000/μL
- Platelets> 75,000/μL
- All grade 2 non-hematologic adverse events (except for fatigue, nausea and vomiting, or laboratory values that are not clinically significant) must have resolved to CTCAE grade 1

10.4 - Tumor and blood samples for correlative/companion studies

All patients enrolled on this study will undergo paired biopsies/blood samples for research purposes (correlative/companion studies) where feasible

Blood samples for research purposes will be obtained at week 1 (before treatment), 4, 7, 13, and 22 and at the date of the off study visit (± 3 days). This is detailed in Table 5 (Study calendar). Research blood collection procedures will be performed as outlined in Appendix A.

Biopsies for research purposes will be done at baseline (within 3 weeks of the first dose of epacadostat and/or pembrolizumab) and at Week 7 in all patients enrolled in this study where feasible. Up to 6 cores from each tumor biopsy site should be taken where feasible and safe to do so. An optional biopsy will be offered to all patients at the time of progression. Biopsy procedures will otherwise be performed in accordance with institutional guidelines and the biopsy protocol outlined in Appendix A.

10.4.1 Tumor Based Biomarkers

Interrogation of immune responses within the tumor microenvironment of sarcomas before and after treatment with epacadostat and PD-1 checkpoint blockade.

For each resected specimen, up to 6 cores of tissue will be obtained for tumor immune correlative studies.

a) **Density of immune infiltration and immune checkpoint and kynurenine expression of sarcomas:** IHC will be used to assess the number and composition of immune infiltrates in order to define the immune cell subsets present within the tumor before and after exposure to epacadostat and pembrolizumab. PD-L1, PD-1, ID0-1 and kynurenine expression within the tumor before and after exposure to epacadostat and pembrolizumab will also be determined by IHC.
   The IHC assays will be performed using but are not limited to the following markers: CD3, CD4, CDS, CD25, CD28 CD45RA, CD68, CD69, CCR?, ID0-1, kynurenine, PD-L1, PD-1, CD137, FOXP3, LAG-3, TIM-3, and ICOS. PD-L1 expression by immunohistochemistry staining of archival tumor specimens will be performed with using a QualTek immunohistochemistry-based assay.

b) **Phenotype and function of TIL in human sarcomas:**
   Multiparameter flow cytometry (MFC) performed on freshly dissociated tumor tissue will be used to characterize the tissue T cell populations. We will study the functional significance of PD-1 expression and ID0-1 expression on T cells isolated from sarcomas. Using intracellular cytokine staining (ICS) and MFC analysis on freshly isolated TIL, we will identify the T cell cytokine profiles in

accordance to their immune checkpoint profile (PD-1, LAG-3, TIM-3) and level of IDO-1 expression. A range of cytokines representing key lymphocyte subgroups (e.g., Th1, 2 or 17) such as IL-2, TNF-a, IFN-y IL-17 among other inflammatory mediators will be assessed. Functional T cell markers including granzyme Band perforin as well as activation markers such as CD62L, CD44, CD69 will be also included in our analysis.

c) **Tumor Biopsy gene expression profiling:** Fresh tumor biopsy will be examined for RNA gene and protein expression by NanoString technology (nCounter® RNA: Protein, PanCancer Immune Profiling Panel) and/or qRT-PCR to detect expression of immune related genes. This panel includes 770 immune related genes including: 109 genes related to cell surface markers for 24 different immune cell types and populations, 30 genes for commonly studied cancer/testis (CT) antigens, over 500 genes for measuring immune response and 40 reference genes.

d) **Neoantigen analysis:** Massively parallel sequencing of the whole exome of the tumor tissue and normal blood will be performed for patients who opt in. Genomic DNA will be captured via solution-based hybrid selection and sequenced on the Illumina HiSeq platform by the Genomics Core at MSKCC. The sequencing data will be aligned by the Bioinformatics Core Tumor, using Somatic Sniper, Somatic Indel Detector and Mutect softwares.

e) **Next generation sequencing for T-cell receptor clonality in tumor-infiltrating lymphocytes (TIL):** Samples will be analyzed using highthroughput sequencing of the variable 13-chain of the T cell receptor (TCR) to characterize the expansion and clonality of the T-cell repertoire in TIls.

10.4.2 Peripheral blood studies

Blood samples will be taken prior to initiation of study therapy and on designated time points post-treatment. These samples will be analyzed for:

a.) **Immunophenotyping and Functional Analyses:**

1. Samples will be analyzed by flow cytometry to study the effects of epacadostat and pembrolizumab on various peripheral blood immune cell subsets including, but not limited to T cell subsets (activated, memory and regulatory T cells).
2. To explore whether inhibition of both PD-1 and IDO-1 in combination will restore T cell activation and function, peripheral blood mononuclear cells (PBMCs) will be isolated and cryopreserved. Assays of the functional status of effector T cells will

be performed, including, but not limited to assays for interferon-gamma (IFN-y) and granzyme B. This assay will use a non-specific stimulus including but not limited to anti-CD3 and anti-CD28 and would allow for the comparison of the effect of PD-1 blockade alone on T cell function.

b.) Soluble Factors: Baseline and on-treatment serum levels of chemokines, cytokines and other immune mediators will be assessed by techniques that may include but are not limited to ELISA or multiplex assays. Analytes may include, but are not limited to IFN-y, IL-12, IL-10, soluble MICA, C-reactive protein, soluble PD-1 and soluble PD-L1.

c.) Next generation sequencing for T-cell receptor clonality in peripheral blood: Samples will be analyzed using highthroughput sequencing of the variable 13-chain of the T cell receptor (TCR) to characterize the expansion and clonality of the T-cell repertoire in peripheral blood mononuclear cells.

Table 4. Exploratory Biomarkers

Biomarker name	Assay	Tissue/Body Fluid Tested and Timing of Assay
Peripheral Blood Cells	1. Flow cytometric analyses to evaluate activated (HLA-DR+) and memory (CD45RA-) T cells 2. Flow cytometric analyses to evaluated peripheral blood leucocytes including CD4/CD25/FoxP3, CD4/CD8/CD45RA/CCR7, CD4/CD8/LAG3/PD-1/PD-L1, CD4/CD8/CD137/IDO-1 3. Functional Status of effector T cells assays for interferon-gamma and granzyme B. 4. T-cell subsets and their activation status (CDS+ Teff/Treg ratio and ICOS expression	Blood (Weeks 1(before treatment), 4, 7, 13, 22 and off-study)
Soluble Factors, Serum	Treatment modulation of serum levels of chemokines, cytokines and other immune mediators by ELISA or other multiplex-based assay methods. Primary analysis includes interferon-gamma and IL-10.	Blood Serum (Weeks 1(before treatment), 4, 7, 13, 22 and off-study)
Characterization of Tumor infiltrating lymphocytes	1. IHC to assess number and composition of immune infiltrates to define immune cell subsets present within	Tumor biopsy at: Baseline

	tumor before and after exposure to treatment. CD3, CD4, CD8 and FOXP3 will be evaluated. 2. Immune cell phenotyping of freshly isolated TIL to evaluate Treg/Teff ratio (CD8+/FoxP3+ cells) and activations markers (ICOS, PD-1, CD69).	Week 7 Progression (optional)
100- 1, PD-L1 & kynurenine expression by IHC	Qualtek immunohistochemistry-based assay for PD-L1	Tumor biopsy at: Baseline Week 7 Progression (optional)
Tumor Biopsy neoantigen analysis	Fresh frozen tumor biopsy will be utilized for massively parallel whole exome sequencing. Available databases such as SNP effect (http://snpeff.sourceforge.neUwill be used to determine which mutations are in coding regions and will affect amino acid sequence. NetMHC and the Immune Epitope Database will be utilized to predict **MHC** Class I binding and T cell interactions, respectively.	Tumor biopsies at baseline Paired normal peripheral blood mononuclear cells at baseline
T-cell receptor sequencing	Highthroughput sequencing of the variable (3 chain of the T-cell receptor.	Tumor biopsy at: Baseline Week 7 Progression (optional)

Table 5. Study calendar -

	Screening	Cycle 1			Cycle 2			Cycle 3			Off study visit[1]
		Wk1	Wk2	Wk3	Wk4	Wk5	Wk6	Wk7	Wk8	Wk9	
EpacadostatA		X	X	X	X	X	X	X	X	X	
Pembrolizumab[8]		X			X			X			
Informed consent	X										
Pathologic Confirmation at study siteJ	X										
Review of concomitant medications	X	X			X			X			
Review of adverse events		X			X			X			X
Physical exam	X	X			X			X			X
Routine laboratory testsc	X	X			X			X			X
Research blood tests[0]		X			X			X			X
Hepatitis B, C and HIV	X										
Pregnancy TestE	X										X
ECGF	X								X		X
ECHO	X										
CT and/or **MRI**[8]	X								X		
Biopsy	X							X			

A. Epacadostat will be administered twice daily, orally, continuously from day 1-21 (inclusive) of each treatment cycle, each treatment cycle consists of 21 days
B. Pembrolizumab will be administered once at a dose of 200mg, intravenously, on day 1 of cycle **1** and every 3 weeks (±3 days) thereafter
C. Routine laboratory tests at screening, day 1 of cycle 1 and then prior to every scheduled treatment visit(± 3 days) thereafter. All routine blood samples should be obtained prior to the daily dose epacadostat and/or pembrolizumab. routine laboratory tests include: cbc with differential, PT/INR and a PTT, comprehensive metabolic panel, magnesium and phosphorus, fT4, TSH, T3, lipase and amylase
D. Research blood samples will be collected at week 1 (before treatment), 4, 7,13, 22 and at the date of the off study visit(± 3 days)

E. Serum pregnancy test (Female subject of childbearing potential should have a negative serum pregnancy at screening and within 72 hours prior to receiving the first dose of both study drugs and at the off study visit.)
F. An ECG will be performed at baseline, week 8, every 8 weeks subsequently((± 1 week window) and at the off study visit((± 1 week window)

G. Standard Imaging studies will be performed at baseline, week 8 and every 8 weeks subsequently (± 1 week window) until 56 weeks, and then every 12 weeks thereafter or as per the discretion of the treating investigator and will include CT of chesUabdomen/pelvis and MRI of the affected area if deemed necessary by the study investigator.
H. Optional biopsy at progression.
I. The off study visit will take place 30 days(+/- 7 days) after the last dose of study therapy
J. Pathologic confirmation of the presence of sarcoma at the study site may take place during or before the screening period.

11.0 TOXICITIES/SIDE EFFECTS

Toxicity will be assessed using the NCI CTCAE (version 4.03). (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

Patients who have received at least one dose of the epacadostat and/or pembrolizumab are available for the safety assessment. Patients who discontinue the study before receiving their first dose of the study treatments will not be available for safety assessment and should be replaced.

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value must be followed until resolution or stabilization of the event.

A dose delay >6 weeks from the date of the planned dose (i.e., approximately 9 weeks since the previous dose) may require the patient to be discontinued from the study, with exception of patients who undergo surgery. A dose delay >6 weeks from the date of the planned dose (i.e., approximately 9 weeks since the previous dose) due to the occurrence of an adverse event that is considered related to epacadostat and/or pembrolizumab, the subject should be taken off study treatment.

11.1 Adverse Event Characteristics and Definitions

11.1.1 Definition of an AE

Any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits, abuse, or misuse. Examples of events meeting the definition of an AE include:

• Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or grade of the condition

• New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study

• Signs, symptoms, or the clinical sequelae of a suspected interaction

• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE).

Events that do not meet the definition of an AE include:

• Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.

• Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

• Anticipated day-to-day fluctuations of pre-existing disease or condition present or detected at the start of the study that do not worsen.

• The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

11.1.2 Definition of a SAE

A serious adverse event is any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is

serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an SAE.

d. Results in disability/incapacity, or

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect.

f. All grade 4 laboratory abnormalities

g. Specific liver function abnormalities and pregnancy

Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

11.1.3 Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis), or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements) including those that worsen from baseline, and events felt to be clinically significant in the medical and scientific judgment of the investigator are to be recorded as an AE or SAE, in accordance with the definitions provided.

However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are not to be reported as AEs or SAEs.

11.1.4 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

Disease Related Events are events (serious or non-serious) anticipated to occur in the study population due to the underlying disease. These could include overall disease progression or pain or discomfort caused by growing tumors. Such events do not meet the definition of an Adverse Event unless assessed to be more severe than expected for the subject's condition.

An event which is part of the natural course of the disease under study (i.e., disease progression) does not need to be reported as an SAE. Deaths and hospitalizations related to disease (other than for study procedures) during the study period and 30 days after completion must be reported as SAEs.

Disease Related Events that would qualify as an Adverse Event or Serious Adverse Event:

- An event based on the underlying disease that is worse than expected as assessed by the investigator for the subject's condition

The investigator believes there is a causal relationship between the investigational product[33]/study treatment/protocol required therapies and disease worsening

11.2 Risks, toxicities and adverse drug reactions - Epacadostat

Epacadostat dosing likely will produce side effects, and not all side effects may be known. Specific identified risks and potential risks are highlighted below, as well as adverse drug reactions observed in clinical trials.

See the investigation brochure for complete list of possible adverse events related to epacadostat.

11.2.1 Identified Risks - Epacadostat

Monotherapy

In the Phase 1 clinical study in subjects with refractory solid tumors (INCB 24360-101), epacadostat was well tolerated at doses ranging from 50 mg QD to 700 mg BID. Twenty-five (48.1%) of the 52 subjects administered epacadostat had a single SAE. The most frequently reported SAEs were disease progression (4 subjects, 7.7%), followed by abdominal pain, nausea, and hypoxia (3 subjects each, 5.8%). Treatment-emergent adverse events (TEAEs) were reported in all subjects. The most commonly reported treatment-related TEAEs were fatigue and nausea (25 subjects, 48.1%). The incidence and severity of fatigue were not dose-related. Two DLTs occurred: 1 DLT of radiation pneumonitis at the 300 mg dose level and 1 DLT of fatigue at the 400 mg BID dose level.

Data from Study INCB 24360-210 (600 mg BID of epacadostat versus 20 mg BID of tamoxifen in Stage III or IV epithelial ovarian cancer) are available as of the data cutoff on 29 OCT 2014. At the time of the cutoff, 42 subjects were enrolled (22 in the epacadostat-treated group and 20 in the tamoxifen-treated group). Based on the preliminary unaudited data through that date, no subject had an AE leading to death. Two

subjects (4.8%) had an SAE. One SAE was reported in the epacadostat group (abdominal pain), and 1 SAE was reported in the tamoxifen group (ascites). Treatment-emergent AEs were reported in 32 subjects (76.2%) with 17 subjects (77.3%) in the epacadostat group and 15 subjects (75.0%) in the tamoxifen group. Fatigue was the most frequently reported TEAE in the epacadostat group (8 subjects, 36.4%), followed by nausea (6 subjects, 27.3%) and abdominal distention, constipation, and vomiting (4 subjects each, 18.2%). This study has been terminated by Incyte. No new safety concerns with epacadostat were identified.

Combination Therapy

Preliminary data from Study INCB 24360-201 (evaluating the combination of epacadostat and ipilimumab) suggest that epacadostat 50 mg BID is well tolerated with ipilimumab based on evaluation of subjects in 50 mg BID continuous cohort. Only 4 of the 18 evaluable subjects reported DLTs, which included a Grade 3 diarrhea (n = 1), a Grade 3 ALT/AST elevation (n = 1), a Grade 3 colitis (n = 1), and a Grade 3 pneumonitis (n = 1). One of the 9 subjects enrolled in 50 mg BID intermittent cohort reported Grade 3 colitis as a DLT. The most common irAEs with Grade 3 were AST elevation and colitis (n = 4, 9.5% each) and ALT elevation (n = 3, 7.1%). Other irAEs with Grade 3 observed in only 1 subject were idiopathic thrombocytopenic purpura, diarrhea, acute renal failure, pneumonitis, pruritus, and rash (2.4% each). Common treatment emerging AEs reported included fatigue (n = 29, 69%), constipation and nausea (n = 13, 31% each), decreased appetite and headache (n = 11, 26% each), and vomiting (n = 10, 24%). This study is currently closed to enrollment.

The initial evaluation of epacadostat 300 mg BID in combination with ipilimumab was terminated because of the occurrence of Grade 3 or 4 alanine aminotransferase (ALT)/aspartate aminotransferase (AST) elevation in 5 of 7 subjects treated at this dose. The most common Grade 1 or 2 AEs reported at 25 mg BID (N = 8) were fatigue (n = 6, 75%), abdominal pain (n = 6, 75%), headache (n = 5, 62.5%), rash (n = 4, 50%), nausea (n = 4, 50%), cough (n = 4, 50%), and diarrhea (n = 3, 37.5%). Grade 3 or 4 AEs that occurred in > 1 subject at 25 mg BID were colitis (Grade 3) and elevated alkaline phosphatase (Grade 3), with n = 2 each (25%).

As of the data cut off (28 MAR 2016), 60 subjects have been enrolled in INCB 24360-202 (epacadostat 25 mg, 50 mg, 100 mg, and 300 mg BID in combination with pembrolizumab). Based on the preliminary unaudited safety data (unaudited), no Grade 4 treatment related AEs were reported. Three subjects (5%) discontinued for a treatment-related AE: Grade 3 arthralgia, Grade 3 AST elevation, and Grade 2 nervous system disorder. No treatment-related deaths occurred. Treatment-emergent AEs were reported in 44 subjects (73.0%). The most frequently reported AEs were rash (27%) followed by fatigue (23%). Rash includes the preferred terms rash, rash generalized, rash maculopapular, rash pruritic, and rash follicular. As of the data cutoff (28 MAR 2016), 18 subjects in the Phase 1 portion of the INCB 24360-202 study and 119 subjects in the Phase 2 portion of the study have received combination treatment with pembrolizumab and the 100 mg BID dose of epacadostat, the recommended dose for the Phase 3 study. The data for Phase 2 presents a subset of 99 subjects who had at least 1 month of safety data. The most frequently reported (15%) AEs of any grade for the combined Phase 1

and Phase 2 subjects treated with epacadostat 100 mg BID were fatigue (35.0%), constipation (24.8%), diarrhea (20.5%), nausea (20.5%), vomiting (18.8%), pyrexia (16.2%), and dyspnea (15.4%). Fatigue (13.7%) and rash (11.1%; including the preferred terms rash, rash maculopapular, rash generalized, and rash macular) were the only treatment-related AEs reported in > 10% of subjects. Treatment-related AEs of rash were only reported in Phase 2. Treatment-related AEs 2: Grade 3 occurring in more than 1 subject who received epacadostat 100 mg BID in Phase 1 or Phase 2 included rash (5 subjects, 4.3%) and dehydration, lipase increased, AST increased, and nausea (2 subjects [1.7%] each). Theoretically, inhibition of IDO1 could cause an increase in serotonin levels that could precipitate a cluster of AEs termed serotonin syndrome (SS) when administered alone or in combination with other serotonergic agents. This rare syndrome has been associated with some monoamine oxidase inhibitors (MAOIs) and combinations of serotonergic drugs. The clinical manifestations of SS range from barely perceptible to lethal; onset is rapid (within 12 hours of drug[s] administration). Based on preliminary studies in the rat, concentrations of epacadostat in the cerebrospinal fluid were below the quantifiable limit of detection (2 nM) after IV dosing, and total brain homogenate concentrations were approximately 15% of corresponding plasma concentrations. Therefore, epacadostat exhibits apparent limited penetration across the blood-brain barrier and is likely not associated with significant effects on tryptophan metabolism in the brain that might affect brain serotonin levels. In the INCB 24360-201 study, 12 of the 48 subjects enrolled as of 29 OCT 2014 received concomitant treatment with an SSRI and epacadostat, and O of 12 subjects exhibited SS. Although this represents a hypothetical risk only and has not been observed in clinical studies of epacadostat, use of MAOIs will be prohibited during the study, and all subjects will be assessed for SS symptoms at an appropriate timeframe after dose administration. Subjects will be provided with an informative subject leaflet describing the signs and symptoms of the syndrome along with instructions to seek immediate medical care if any of these signs or symptoms is observed.

Risk: Serotonin Syndrome

Procedure 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 SS (http://www.nejm.org/doi/full/10.1056/NEJMra041867) 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. Selective serotonin reuptake inhibitors (SSRIs) and serotonin/norepinephrine reuptake inhibitors (SNRIs) are permitted in the study. The following procedures will be implemented if subjects exhibit the signs/symptoms of SS described in Table 6, including tremor; hyperreflexia; and 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.

Table 6: Sign and Symptoms of Serotonin Syndrome

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

Adverse Drug Reactions - Epacadostat

As of 29 Oct 2016, 898 unique subjects have been exposed to INCB024360 in Incyte sponsored studies as monotherapy (149 subjects) and/or in combination with checkpoint inhibitors (anti-PD-1 targeted therapy [543 subjects]); **PD-L**1-targeted therapy (124 subjects); anti-CTLA-4 targeted therapy (50 subjects); and a JAK inhibitor with JAK1 selectivity (32 subjects).

Table 7. contains a list of expected treatment-emergent adverse events for epacadostat monotherapy

Table 7: Expected Treatment-Emergent Adverse Events for Epacadostat Monotherapy

System. Organ Class MedDRA Preforred Term	OveraU Frequency All Grades N(%}	G1·ad1'3 or Gr:acle 4 N{%)	Frequency of Serious E,,ents N(%>)
Gasfroiotl'sfinal di<Jordl't·s			
Dianhea	Very common -19 (12..8)	-	-
Nausea	Very common- 44 (29.5)	Common-5 (3.4)	Connnon.- 3 (2.0)
Vomiting	Vei:ycommon-27 (18.1)	Common - 4 ,(2.7)	Common - 2 (1.3)
Gen.eraJ dirorde1·s and adminisfration. site c,onditions			
Asthenia	Comm.on - 2 (L3)	-	-
Fatigue	Very common- 50 (33_6)	Common - 6 (4.0)	-
lnves1ti.gatioos			
Al.mine aminotransferase increased	Common - 4 (2.7)	Common - 2 (1.3)	-
Aspartate aminotnmsfense incre.as:ed	Common - 4 (2_7)	Uncommon - 1 (0.7)	-
1\{usculoskeletal and c ollD.ectrive tissue disorders			
Arthralgia	Co:mmon - 6 (4.0)	-	-
Skin and subcutaneous tissue diso rders			
Pruritus	Common - 4 (2_7)	-	-
Rash	Common - 5 (3.4)	-	-
Rash maculo-papular	Common - 5 (1.4)	Common - 2 (1.3)	-
Rash papnlar	Common - 2 (1-3)	-	-

'"-"=:not expected.

Table 8. Expected TEAEs for Epacadostat and Anti-PD-1 Combination Therapy (n=543)

System. Organ Class **M:l'ddRA P:n fen:ed Term**	Overall Fl·equency All Grades - (%)	Grade 3 or G1·ade 4 (%)	Fn:iquency of Serious Events - (%)
Endocrine cli.sm·der:s			
Adcenal insufficiency	Unco.mmon-2 (0.4)	Uncomm.011- I (0.2)	-
Hypothyroidism	Common-16 (4.8)	-	-
G3sh·ointestinal disorders			
DiMrhea	Verycommon-103 (19.0)	Common - 8 (1.5)	Uncommon - 4 (0.7)
Nausea	VeryCOlllllllOll- 145(26.7)	Common - 9 (1.7)	Comm.on-13 (2.4)
Vomiting	Veryaommon-101 (l&.6)	Common-10 (L&)	Common - *9* {L 7)
GeneraJ disordea·s and 3 dminisjration site conditions			
Astheni.a	Comwon-31 (:'.i7)	Common- 7 (1.3)	Common- 6(1.1)
Fatigue	Veryaommon-230 (42.4)	Common-11 (20)	Uncommon - 5 ,(0.9)

System Organ Class MedDRA Preferred Term	Overall Frequency All Grades N (%)	Grade 3 or Grade 4 N (%)	Frequency of Serious Events N (%)
Investigations			
Alanine aminotransferase increased	Common – 47 (8.7)	Common – 8 (1.5)	–
Aspartate aminotransferase increased	Very common – 56 (10.3)	Common – 9 (1.7)	–
Musculoskeletal and connective tissue disorders			
Arthralgia	Very common – 60 (11.1)	Uncommon – 3 (0.6)	–
Respiratory, thoracic, and mediastinal disorders			
Pneumonitis	Uncommon – 5 (0.9)	Uncommon – 1 (0.2)	Uncommon – 2 (0.4)
Skin and subcutaneous tissue disorders			
Pruritus	Very common – 72 (13.3)	Uncommon – 3 (0.6)	–
Pruritus generalized	Common – 7 (1.3)	–	–
Rash	Very common – 86 (15.8)	Common – 16 (2.9)	Uncommon – 2 (0.4)
Rash generalized	Common – 13 (2.4)	Uncommon – 2 (0.4)	–
Rash macular	Uncommon – 3 (0.6)	Uncommon – 2 (0.4)	–
Rash maculo-papular	Common – 37 (6.8)	Common – 20 (3.7)	Uncommon – 4 (0.7)
Rash papular	Uncommon – 5 (0.9)	–	–
Rash pruritic	Common – 10 (1.8)	Uncommon – 1 (0.2)	–
Rash pustular	Uncommon – 2 (0.4)	–	–

"–" = not expected.

Preliminary safety results for the phase I study INCB 24360-202, of epacadostat in combination with pembrolizumab) were presented in a poster presentation and are presented in Table 9; these data have a data cutoff of 07 JUL 2016.[50]
Phase 1 has completed enrollment with a total of 62 subjects. Subjects were treated with epacadostat 25 mg BID (n = 4), 50 mg BID (n = 20), 100 mg BID (n = 18), and 300 mg BID (n = 20) in combination with pembrolizumab 2 mg/kg or 200 mg IV every 3 weeks. Treatment-related AEs were reported in 50 subjects (81%). Table 9 presents treatment-related AEs 5% or Grade 3/4 AEs in 1 subject in the Phase 1 portion of the study. The most frequently reported treatment-related AEs were fatigue and rash (29% each). Rash includes the preferred terms rash, rash erythematous, rash generalized, rash maculo-papular, rash pruritic, and rash follicular. The most frequently reported Grade 3 treatment-related AE was rash (8%).
Five subjects (8%) discontinued for a treatment-related AE: Grade 3 arthralgia, Grade 3 AST increased/Grade 2 ALT increased, Grade 3 lipase increased, Grade 3 aseptic meningitis, and Grade 2 nervous system disorder. No treatment-related deaths occurred as of 07 JUL 2016.

Table 9: Related TEAEs 5% or Grade 3 / 4 TEAEs in 1 subject in the phase I population in study INCB 24360-202

Adverse Event, n (%)	All Grades (N = 62)	≥ Grade 3 (N = 62)
Total	50 (81)	12 (19)
Fatigue	18 (29)	0 (0)
Rash[a]	18 (29)	5 (8)
Pruritus[b]	14 (23)	0 (0)
Arthralgia	12 (19)	1 (2)
Diarrhea	11 (18)	0 (0)
Nausea	10 (16)	1 (2)
Pyrexia	7 (11)	0 (0)
Vomiting	7 (11)	1 (2)
AST increased	5 (8)	1 (2)
Chills	5 (8)	0 (0)
Dizziness	5 (8)	0 (0)
Myalgia	5 (8)	0 (0)
Constipation	4 (6)	0 (0)
Headache	4 (6)	1 (2)
Lipase increased	3 (5)	3 (5)
Amylase increased	2 (3)	2 (3)
Anxiety	2 (3)	1 (2)
Mucosal inflammation	2 (3)	1 (2)
Meningitis aseptic	1 (2)	1 (2)

AE = adverse event; AST = aspartate aminotransferase.
[a] Rash includes the following MedDRA preferred terms: rash, rash erythematous, rash generalized, rash maculo-papular, rash pruritic, and rash follicular.
[b] Pruritus includes the following MedDRA preferred terms: pruritus and pruritus generalized.

The combination of epacadostat and pembrolizumab is under investigation in the setting of melanoma, in a phase III study, INCB 24360-301. The recommended phase III dose for this study was based on findings from phase I and phase II of study INCB 24360-202. The preliminary safety results summarized below are the basis for the initial recommended dose in melanoma of epacadostat 100 mg BID in combination with pembrolizumab 200 mg IV Q3W; these data have a data cutoff of 28 MAR 2016.

Eighteen subjects in the Phase 1 portion of the study and 119 subjects in the Phase 2 portion of the study have received at least 1 dose of combination treatment with pembrolizumab and the 100 mg BID dose of epacadostat. The data for Phase 2 provides a subset of 99 subjects who had at least 1 month of safety data. Subjects were included in the data presented below if they were enrolled and received at least 1 dose of study medications on or before 28 FEB 2016 with a data cutoff of 28 MAR 2016 for all subjects. Of the 119 subjects, 115 had the following cancers: melanoma (n = 7), PD-L1-positive NSCLC (n = 5), PD-L1-negative/indeterminate NSCLC (n = 4), transitional cell carcinoma of the genitourinary tract (n = 21), TNBC (n = 24), ovarian cancer (n = 35), DLBCL (n = 3), and SCCHN (n = 16). At the time of the data cutoff, the disease history information for the 4 remaining subjects had not yet been specified in the database.

Table 10 presents an overall summary of TEAEs for subjects administered epacadostat 100 mg BID in the Phase 1 or Phase 2 cohorts of the study.

Table 10: Summary of Treatment-Emergent Adverse Events in Study INCB 24360-202 (Data Cutoff 28 MAR 2016)

Variable, n (%)	Epacadostat 100 mg BID (Phase 1)[a] (n = 18)	Epacadostat 100 mg BID (Phase 2)[b] (n = 99)	Epacadostat Total 100 mg BID (N = 117)
Number of TEAEs reported	219	570	789
Subjects who had at least 1 TEAE	17 (94.4)	85 (85.9)	102 (87.2)
Subjects who had at least 1 TEAEs ≥ Grade 3	9 (50.0)	30 (30.3)	39 (33.3)
Subjects who had at least 1 treatment-related TEAE	16 (88.9)	46 (46.5)	62 (53.0)
Subjects who had at least 1 treatment-related TEAE ≥ Grade 3	4 (22.2)	15 (15.2)	19 (16.2)
Subjects who had at least 1 SAE	8 (44.4)	19 (19.2)	27 (23.1)
Subjects who had at least 1 treatment-related SAEs	3 (16.6)	5 (5.0)	8 (6.8)
Subjects who had a fatal AE	1 (5.6)	2 (2.0)	3 (2.6)

[a] In combination with pembrolizumab 2 mg/kg IV Q3W or 200 mg IV Q3W.
[b] In combination with pembrolizumab 200 mg IV Q3W.

For subjects receiving 100 mg BID in the Phase 1 and Phase 2 portion of the study, 3 subjects died because of AEs. One subject with SCCHN was admitted to the intensive care unit with worsening mental status and prior aspiration pneumonia, and the subject had upper airway hemorrhage and died. A second subject with metastatic urothelial cancer was found unresponsive at home and had been hypoxic for an estimated 35 minutes. The subject was admitted to the hospital and placed on a ventilator (Grade 4 respiratory distress). The subject was later removed from life support and died. A third subject with ovarian cancer reported dehydration and failure to thrive (Grade 4) as AEs with fatal outcome.

Treatment-related TEAEs per investigator occurred in 16 subjects (88.9%) in Phase 1 and 46 subjects (46.5%) in Phase 2. In Phase 2, treatment-related rash (including the preferred terms rash, rash maculopapular, rash generalized, and rash macular) occurred in 13 subjects (13.1%). Other frequently reported treatment-related TEAEs in Phase 2 were fatigue (11.1%); pyrexia (6.1%); and nausea, AST increased, pruritus, and vomiting (4.0% each). Diarrhea, chills, ALT increased, decreased appetite, and arthralgia were each observed in 3 subjects (3.0%). Frequently reported (> 15%) treatment-related AEs in Phase 1 were fatigue (27.8%), AST increased (22.2%), diarrhea (22.2%), vomiting (22.2%), arthralgia (22.2%), nausea (16.7%), and ALT increased (16.7%). Treatment-related TEAEs Grade 3 occurring in more than 1 subject in Phase 2 included rash (5.1%) and dehydration (2.0%). In Phase 1, the only treatment-related TEAE Grade 3 occurring in more than 1 subject was lipase increased in 2 subjects.
The overall incidence of SAEs was 23.1% subjects treated with epacadostat 100 mg BID,

with 44.4% occurring in Phase 1 subjects and 19.2% occurring in Phase 2 subjects. The overall incidence of treatment-related SAEs was 6.8% subjects treated with epacadostat 100 mg BID, with 16.6% occurring in Phase 1 subjects and 5% occurring in the Phase 2 subjects.

Adverse events that were treatment-related and potentially immune-related were observed less frequently in the 99 subjects in Phase 2 in this analysis, except for rash (13.1%) and pruritus (4.0%), compared with the 18 Phase 1 subjects. Of note, no cases of pneumonitis, colitis, or adrenal insufficiency were observed in either the Phase 1 or 2 subjects receiving epacadostat 100 mg BID in combination with pembrolizumab (see Table 11). As of 28 MAR 2016, the Phase 1 group had 1 additional immune-related AE, a single report of Grade 1 hypothyroidism.

Liver enzyme abnormalities, which may be symptoms of a potential immune-mediated liver event, were reported as AST increased in 4 subjects (22%) in Phase 1 and 4 subjects (4.0%) in Phase 2. Three (2.6%) of 8 AST increases were Grade 3. Alanine aminotransferase increased was reported in 3 subjects (16.7%) in Phase 1 and 3 subjects (3.0%) in Phase 2 with only 1 (0.9%) Grade 3 ALT increase. Blood alkaline phosphatase increased was reported in 1 subject (5.6%; Grade 2) in Phase 1 and none in Phase 2. Two subjects required dose interruptions due to ALT or AST increases and 2 subjects required dose discontinuation due to ALT or AST increases. One of the 2 subjects who discontinued treatment due to ALT/AST increases received corticosteroids.

Although the incidence of AEs is lower in the subjects in the Phase 2 portion of the study, it is important to note that subjects in the Phase 1 portion of the study have had a longer duration of exposure (mean 222.0 days vs 62.0 days).

Table 11: Summary of Treatment-Related Potential Immune-Related Adverse Events at 100 mg BID (Data Cutoff 28 MAR 2016)

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

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

With the additional 5 months of follow-up for the subjects treated with 100 mg BID in Phase 1 (median duration of treatment= 222 days), the AE profile remains similar to that originally described. No new safety trends were observed, and the data supports the selected dose of

epacadostat 100 mg BID in combination with pembrolizumab 200 mg IV Q3W in the Phase 3 INCB 24360-301 study.

11.3 - Risks, toxicities and adverse drug reactions - Pembrolizumab

Pembrolizumab dosing likely will produce side effects, and not all side effects may be known. Specific identified risks and potential risks are highlighted below, as well as adverse drug reactions observed in clinical trials:

Information extracted from Pembrolizumab Prescribing Information, available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125514lbl.pdf

11.3.1 - Identified risks - Pembrolizumab

Risk: Immune-Mediated Pneumonitis
Pneumonitis occurred in 12 (2.9%) of 411 melanoma patients, including Grade 2 or 3 cases in 8 (1.9%) and 1 (0.2%) patients, respectively, receiving pembrolizumab. The median time to development of pneumonitis was 5 months (range 0.3 weeks-9.9 months). The median duration was 4.9 months (range 1 week-14.4 months). Five of eight patients with Grade 2 and the one patient with Grade 3 pneumonitis required initial treatment with high-dose systemic corticosteroids (greater than or equal to 40 mg prednisone or equivalent per day) followed by a corticosteroid taper. The median initial dose of high-dose corticosteroid treatment was 63.4 mg/day of prednisone or equivalent with a median duration of treatment of 3 days (range 1-34) followed by a corticosteroid taper. Pneumonitis led to discontinuation of pembrolizumab in 3 (0.7%) patients. Pneumonitis completely resolved in seven of the nine patients with Grade 2-3 pneumonitis.

Risk: Immune-Mediated Colitis
Colitis (including microscopic colitis) occurred in 4 (1%) of 411 patients, including Grade 2 or 3 cases in 1 (0.2%) and 2 (0.5%) patients, respectively, receiving pembrolizumab. The median time to onset of colitis was 6.5 months (range 2.3-9.8). The median duration was 2.6 months (range 0.6 weeks-3.6 months). All three patients with Grade 2 or 3 colitis were treated with high-dose corticosteroids (greater than or equal to 40 mg prednisone or equivalent per day) with a median initial dose of 70 mg/day of prednisone or equivalent; the median duration of initial treatment was 7 days (range 4-41), followed by a corticosteroid taper. One patient (0.2%) required permanent discontinuation of pembrolizumab due to colitis. All four patients with colitis experienced complete resolution of the event.

Risk: Immune-Mediated Hepatitis

Hepatitis (including autoimmune hepatitis) occurred in 2 (0.5%) of 411 patients, including a Grade 4 case in 1 (0.2%) patient, receiving pembrolizumab. The time to onset was 22 days for the case of Grade 4 hepatitis which lasted 1.1 months. The patient with Grade 4 hepatitis permanently discontinued pembrolizumab and was treated with high-dose (greater than or equal to 40 mg prednisone or equivalent per day) systemic corticosteroids followed by a corticosteroid taper. Both patients with hepatitis experienced complete resolution of the event.

Risk: Immune-Mediated Hypophysitis
Hypophysitis occurred in 2 (0.5%) of 411 patients, consisting of one Grade 2 and one Grade 4 case (0.2% each), in patients receiving pembrolizumab. The time to onset was 1.7 months for the patient with Grade 4 hypophysitis and 1.3 months for the patient with Grade 2 hypophysitis. Both patients were treated with high-dose (greater than or equal to 40 mg prednisone or equivalent per day) corticosteroids followed by a corticosteroid taper and remained on a physiologic replacement dose.

Risk: Renal Failure and Immune-Mediated Nephritis
Nephritis occurred in 3 (0.7%) patients, consisting of one case of Grade 2 autoimmune nephritis (0.2%) and two cases of interstitial nephritis with renal failure (0.5%), one Grade 3 and one Grade 4. The time to onset of autoimmune nephritis was 11.6 months after the first dose of pembrolizumab (5 months after the last dose) and lasted 3.2 months; this patient did not have a biopsy. Acute interstitial nephritis was confirmed by renal biopsy in two patients with Grades 3-4 renal failure. All three patients fully recovered renal function with treatment with high-dose corticosteroids (greater than or equal to 40 mg prednisone or equivalent per day) followed by a corticosteroid taper.

Risk: Immune-Mediated Hyperthyroidism and Hypothyroidism
Hyperthyroidism occurred in 5 (1.2%) of 411 patients, including Grade 2 or 3 cases in 2 (0.5%) and 1 (0.2%) patients, respectively, receiving pembrolizumab. The median time to onset was 1.5 months (range 0.5-2.1). The median duration was 2.8 months (range 0.9 to 6.1). One of two patients with Grade 2 and the one patient with Grade 3 hyperthyroidism required initial treatment with high-dose corticosteroids (greater than or equal to 40 mg prednisone or equivalent per day) followed by a corticosteroid taper. One patient (0.2%) required permanent discontinuation of pembrolizumab due to hyperthyroidism. All five patients with hyperthyroidism experienced complete resolution of the event. Hypothyroidism occurred in 34 (8.3%) of 411 patients, including a Grade 3 case in 1 (0.2%) patient, receiving pembrolizumab. The median time to onset of hypothyroidism was 3.5 months (range 0.7 weeks-19 months). All but two of the patients with hypothyroidism were treated with long-term thyroid hormone replacement therapy. The other two patients only required short-term thyroid hormone replacement therapy. No patient received corticosteroids or discontinued pembrolizumab for management of hypothyroidism.

Risk: Infusion reactions

Pembrolizumab infusion reactions may consist of fever, chills/rigor, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria!, rash, vomiting, myalgia, dizziness, or hypertension. Severe reactions may include acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock. Patients should be closely monitored for such reactions. Guidelines for patients who experience an infusion related or allergic reaction during or after infusion with pembrolizumab are detailed in Table 17..

Risk: Other Immune-Mediated Adverse Reactions
Other clinically important immune-mediated adverse reactions can occur. The following clinically significant, immune-mediated adverse reactions occurred in less than 1% of patients treated with pembrolizumab: exfoliative dermatitis, uveitis, arthritis, myositis, pancreatitis, hemolytic anemia, partial seizures arising in a patient with inflammatory foci in brain parenchyma, and adrenal insufficiency. Other adverse events of interest have been reported in patients after treatment with pembrolizumab including myocarditis, Stevens Johnson Syndrome (SJS) and Toxic Epidernal Necrolysis (TEN). Of note fatal outcomes have been reported in some of the cases of SJS and TEN that occurred in patients treated with pembrolizumab.

Across clinical studies with pembrolizumab in approximately 2000 patients, the following additional clinically significant, immune-mediated adverse reactions were reported in less than 1% of patients: myasthenic syndrome, optic neuritis, and rhabdomyolysis.

11.3.2 - Adverse Drug Reactions - Pembrolizumab

Adverse drug reactions observed in an uncontrolled, open-label, multiple cohort trial in which 411 patients with unresectable or metastatic melanoma received pembrolizumab at either 2 mg/kg every 3 weeks or 10 mg/kg every 2 or 3 weeks (Trial 1). The median duration of exposure to pembrolizumab was 6.2 months (range 1 day to 24.6 months) with a median of 10 doses (range 1 to 51).

Pembrolizumab was discontinued for adverse reactions in 9% of the 411 patients. Adverse reactions, reported in at least two patients that led to discontinuation of pembrolizumab were: pneumonitis, renal failure, and pain. Serious adverse reactions occurred in 36% of patients receiving pembrolizumab. The most frequent serious adverse drug reactions reported in 2% or more of patients in Trial 1 were renal failure, dyspnea, pneumonia, and cellulitis. Table 12 presents adverse reactions identified from analyses of the 89 patients with unresectable or metastatic melanoma who received pembrolizumab 2 mg/kg every three weeks in one

cohort of Trial 1. This cohort of Trial 1 excluded patients with severe immune-related toxicity related to ipilimumab, defined as any Grade 4 toxicity requiring treatment with corticosteroids or Grade 3 toxicity requiring corticosteroid treatment (greater than 10 mg/day prednisone or equivalent dose) for greater than 12 weeks; a medical condition that required systemic corticosteroids or other immunosuppressive medication; a history of pneumonitis or interstitial lung disease; or any active infection requiring therapy, including HIV or hepatitis B or C. Of the 89 patients in this cohort, the median age was 59 years (range 18-88), 33% were age 65 years or older, 53% were male, 98% were white, 44% had an elevated **LOH,** 84% had Stage M1c disease, 8% had brain metastases, and 70% received two or more prior therapies for advanced or metastatic disease. The median duration of exposure to pembrolizumab was 6.2 months (range 1 day to 15.3 months) with a median of nine doses (range 1 to 23). Fifty-one percent of patients were exposed to pembrolizumab for greater than 6 months and 21% for greater than 1 year. Pembrolizumab was discontinued for adverse reactions in 6% of the 89 patients. The most common adverse reactions (reported in at least 20% of patients) were fatigue, cough, nausea, pruritus, rash, decreased appetite, constipation, arthralgia, and diarrhea.

Table 12: Adverse Reactions in 10% of patients with unresectable or metastatic melanoma treated with pembrolizumab 2mg/kg every 3 weeks.

Adverse Reaction	All Grades (%)	Grade 3* (%)
General Disorders and Administration Site Conditions		
Fatigue	47	7
Peripheral Edema	17	1
Chills	14	0
Pyrexia	11	0
Gastrointestinal Disorders		
Nausea	30	0
Constipation	21	0
Diarrhea	20	0
Vomiting	16	0
Abdominal pain	12	0
Respiratory, Thoracic And Mediastinal Disorders		
Cough	30	1
Dyspnea	18	2
Skin And Subcutaneous Tissue Disorders		
Pruritus	30	0
Rash	29	0
Vitiligo	11	0
Metabolism and Nutrition Disorders		
Decreased appetite	26	0
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	20	0
Pain in extremity	18	1
Myalgia	14	1
Back pain	12	
Nervous System Disorders		
Headache	16	0
Dizziness	11	0
Blood and Lymphatic System Disorders		
Anemia	14	5
Psychiatric Disorders		
Insomnia	14	0

Infections and Infestations	
Upper respiratory tract infection	11

There were no Grade 5 adverse reactions reported. Of the 10% adverse reactions, none was reported as Grade 4.

Other clinically important adverse reactions observed in up to 10% of patients treated with pembrolizumab were: *Infections and infestations:* sepsis

Table 13: Laboratory Abnormalities Increased from baseline in 20% of patients with unresectable or metastatic melanoma treated with pembrolizumab 2mg/kg every 3 weeks.

Laboratory Test	All Gradesl %	Grades 3-4 %
Chemistry		
Hyperglycemia	40	2*
Hyponatremia	35	9
Hypoalbuminemia	34	0
Hypertriglyceridemia	25	0
Increased Aspartate Aminotransferase	24	2*
Hypocalcemia	24	1
Hematology		
Anemia	55	8*

* Grade 4 abnormalities in this table limited to hyperglycemia, increased aspartate aminotransferase, and anemia (one patient each)

11.4 Dose adjustments, delays, rules for withholding and restarting treatment and permanent discontinuation.

11.4.1 Epacadostat

Dose reductions/Interruptions - Epacadostat

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

Any interruptions of> 2 weeks or for LFT abnormalities must be discussed with the medical monitor before resuming treatment. Treatment with both study drugs should be withheld for drug-related Grade 4 hematologic toxicities, nonhematological toxicity Grade 3 (including laboratory abnormalities), and severe or life-threatening AEs.

Epacadostat may be dose reduced according to the guidelines and dose levels described in Table 14.

Dosing interruptions may be permitted in the case of medical/surgical events or logistical reasons not related to study therapy (eg, elective surgery, unrelated medical events,

subject vacation, and/or holidays). Subjects will be placed back on study therapy within 3 weeks of the scheduled interruption. The reason for interruption should be documented in the subject's study record.

For patients who do not tolerate the RP2D of epacadostat in combination with pembrolizumab, three dose reductions are permitted (Table 14) in order to allow the patient to continue on study drug. The following guidelines need to be applied and these changes must be recorded on the Dosage Administration Record. Please refer to Table 15 for dose reduction steps and criteria for interruption and re-initiation of epacadostat for drug-related toxicities. Doses held during the study will not be made up. When toxicity that resulted in a dose reduction improves to grade 1 or less, the dose can be re-escalated at the investigators discretion provided there are no other concomitant toxicities.

Table 14 Dose Modification Algorithm for Adverse Events Associated with Epacadostat

Epacadostat Dose Levels	Dose Level 1 (starting dose)	Dose Level -1	Dose Level -2
Actual Dose	100mg bid	50mg bid	25mg bid

Table 15. Dose Modification Guidelines for Epacadostat Related Adverse Effects without Immune Etiology

Toxicity	Grade	Hold Treatment (Y/N)	Timing for Treatment Restart	Dose for Treatment Restart	Discontinue Subject (after discussion with PI)
Hematologic Toxicity	1,2,3	No	N/A	N/A	N/A
	4	Yes	Permanently discontinue treatment	N/A	Permanently discontinue study treatment
Non Hematologic Toxicity	1	No	N/A	N/A	N/A

Note: Exception to be treated to similar Grade 1 toxicity: -G2 alopecia -G2 fatigue	2	Consider holding for persistent symptoms	Toxicity resolves to ::;; grade 1 or baseline	Restart at same dose	Toxicity does not resolve within 12 weeks of last dose of treatment
	3,4	Yes	Toxicity resolves to ::;; grade 1 or baseline. Subjects with AEs that stabilize at grade 2 (such as neuropathy) may resume treatment upon principal investigator approval. Permanent discontinuation of epacadostat in setting of grade 4 toxicities with the exception of grade 4 laboratory abnormalities that are deemed clinically insignificant	Restart at 1 dose level lower	Toxicity does not resolve within 12 weeks of last dose of treatment. Permanent discontinuation should be considered for any severe or life threatening event.
With principal investigator agreement, subjects with a laboratory AE still at grade 2 after 12 weeks may continue treatment in the study only if asymptomatic and controlled.					

Adverse events of a potential immunologic etiology or immune-related AEs (irAEs) 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 compounds, their mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. Special attention should be paid to AEs that may

be suggestive of potential irAEs. An irAE can occur shortly after the first dose or several months after the last dose of treatment.

If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes prior to labeling an AE as an irAE.

Immune-related adverse events may be attributable to epacadostat alone, pembrolizumab alone, or the combination of both agents. If the event is clearly related to one of the agents, follow the instructions specific for that agent. If the event is related to both agents, follow the action taken instructions for both.

Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined in Table 16. below. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

Table 16: Dose Modification Guidance Epacodostat and Pembrolizumab.

Immune-related AEs	Toxicity Grade or Conditions (CTCAEv4.0)	Study Medication	Action Taken with Study Medication	irAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up
Pneumonitis	Grade 2	Pembrolizumab	Withhold until Grade 0-1	• Administer corticosteroids (initial dose of l-2mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
		Epacadostat	Withhold until Grade 0-1 Related: Reduce by 1 dose level. Not Related: Same dose level.		

Immune-related AEs	Toxicity Grade or Conditions (CTCAEv4.0)	Study Medication	Action Taken with Study Medication	irAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up
	Grade 3 or 4, or recurrent grade 2	Pembrolizumab	Permanently discontinue		
		Epacadostat or matching placebo	Permanently discontinue		
Diarrhea / colitis	Grade 2 or 3	Pembrolizumab	**Withhold** until Grade **0-1**	• Administer corticosteroids (initial dose of 1-2mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (i.e. diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e. peritoneal signs and ileus). • Participants with::,: Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be
		Epacadostat	**Withhold** until Grade **0-1** Related: Reduce by 1 dose level. Not Related: Same dose level.		
	Grade 4	Pembrolizumab	Permanently discontinue		
		Epacadostat	Permanently discontinue		

Immune-related AEs	Toxicity Grade or Conditions (CTCAEv4.0)	Study Medication	Action Taken with Study Medication	irAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up
					substituted via IV infusion.
AST/ ALT Elevation or Increased Bilirubin	Grade 2*	Pembrolizumab	**Withhold** until Grade **0-1**	• Administer corticosteroids (initial dose of 0.5- lmg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
		Epacadostat	**Withhold** until Grade **0-1** Related: Reduce by 1 dose level. Not Related: Same dose level.		
	Grade 3 or 4	Pembrolizumab	Permanently discontinue	• Administer corticosteroids (initial dose of l-2mg/kg prednisone or equivalent) followed by taper	
		Epacadostat	Permanently discontinue		
Type 1 diabetes mellitus (T1DM) or Hyperglycemiab	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of p-cell failure	Pembrolizumab	**Withhold** until Grade **0-1**	• Initiate insulin replacement therapy for participants with TlDM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
		Epacadostat	**Withhold** until Grade **0-1** Related: Reduce by 1 dose level.		

Immune-related AEs	Toxicity Grade or Conditions (CTCAEv4.0)	Study Medication	Action Taken with Study Medication	irAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up
			Not Related: Same dose level.		
Hypophysitis	Grade 2	Pembrolizumab	**Withhold** until Grade **0-1**	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
		Epacadostat	**Withhold** until Grade **0-1** Related: Reduce by 1 dose level. Not Related: Same dose level.		
	Grade 3 or 4	Pembrolizumab	**Withhold** until Grade 0- 1 or permanently discontinuea		
		Epacadostat	**Withhold** until Grade 0- 1 or permanently discontinuea Related: Reduce by 1 dose level.		

Immune-related AEs	Toxicity Grade or Conditions (CTCAEv4.0)	Study Medication	Action Taken with Study Medication	irAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up
			Not Related: Same dose level.		
Hyperthyroidismb	Grade 2	Pembrolizumab	Continue	• Treat with non-selective beta-blockers (e.g. propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
		Epacadostat	Continue		
	Grade 3 or 4	Pembrolizumab	**Withhold** until Grade 0- 1 or permanently discontinuea		
		Epacadostat	**Withhold** until Grade 0- 1 or permanently discontinuea Related: Reduce by 1 dose level. Not Related: Same dose level.		
Hypothyroidismb	Grade 2-4	Pembrolizumab	Continue	• Initiate thyroid replacement hormones (e.g. levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
		Epacadostat	Continue		

Immune-related AEs	Toxicity Grade or Conditions (CTCAEv4.0)	Study Medication	Action Taken with Study Medication	irAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up
Nephritis and Renal Dysfunction	Grade 2	Pembrolizumab	Withhold until Grade 0- 1	• Administer corticosteroids (prednisone l-2mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
		Epacadostat	**Withhold** until Grade **0-1** Related: Reduce by 1 dose level. Not Related: Same dose level.		
	Grade 3 or 4	Pembrolizumab	Permanent! y discontinue		
		Epacadostat	Permanent! y discontinue		
Rash	1 or 2	Pembrolizmnab	Continue	• Manage with topical steroids with or without drug interruption.	
		Epacadostat	Continue		
	3 c	Pembrolizumab	Withhold until Grade 0-1	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper.	• If toxicity does not resolve within 12 weeks of last dose, or cannot taper below 10 mg or less of prednisone or equivalent within 12 weeks, must permanently discontinue.
		Epacadostat	Withhold until Grade 0-1		

Immune-related AEs	Toxicity Grade or Conditions (CTCAEv4.0)	Study Medication	Action Taken with Study Medication	irAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up
			Related: Reduce by 1 dose level. Not Related: Same dose level.		• Restart epacadostat at same dose if rash is mild and assessed as Grade 3 based only on body surface area and resolves without oral steroids. If oral steroids are required, or rash is severe, decrease by 1 dose level once resolved to Grade 0-1.
	4	Pembrolizumab	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper.	
		Epacadostat	Permanently discontinue		
Asymptomatic[d] Amylase or Lipase Increased	3	Pembrolizumab	May continue treatment with medical monitor approval		• Pennanently discontinue if clinical signs and symptoms of pancreatitis develop (abdominal pam, nausea, vomiting). • If toxicity does not resolve within 12 weeks of last dose after an interruption, must pennanently discontinue unless approved by the medical monitor to continue.
		Epacadostat	May continue treatment with medical monitor approval		
	4	Pembrolizumab	Withhold until toxicity resolves to Grade 0-1[e]		
		Epacadostat	Withhold until toxicity resolves to Grade 0-1[e] Related: Reduce by		

Immune-related AEs	Toxicity Grade or Conditions (CTCAEv4.0)	Study Medication	Action Taken with Study Medication	irAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up
			1 dose level. Not Related: Same dose level.		• If Grade 4 lipase/amylase elevation is asymptomatic and abdominal imaging suggests no pathology, study drug administration dosing may continue with medical monitor approval.
All Other Immune-related **AEs**	Grade 3, or intolerable/ persistent Grade 2	Pembrolizumab	**Withhold** until Grade 0- 1	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
		Epacadostat	**Withhold** until Grade **0-1** Related: Reduce by 1 dose level. Not Related: Same dose level.		
	Grade 4 or recurrent Grade 3	Pembrolizumab	Permanently discontinue		
		Epacadostat	Permanently discontinue		

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

General Instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab and epacadostat have been withheld, pembrolizumab and epacadostat/placebo can be resumed after AE has been reduced to Grade 1 or O and corticosteroid has been tapered. Pembrolizumab and epacadostat/placebo should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to :S 10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated ifirAEs cannot be controlled by corticosteroids.
4. Pembrolizumab should be permanently discontinued if Stevens Johnson Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN) occurs.

NOTES:

1. Withhold OR permanently discontinue pembrolizumab + epacadostat at the discretion of the Investigator.
2. For participants with Grade 3 or 4 immune-related endocrinopathy where withholding ofpembrolizumab and epacadostat is required, pembrolizumab and epacadostat may be resumed when AE resolves to :S Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case ofTlDM)
3. Participants with Grade 3 rash in the absence of desquamation, no mucosa] involvement, does not require systemic steroids, and resolves to Grade 1 within 14 days does not have to hold study medication
4. If Grade 4 lipase/amylase elevation is asymptomatic and abdominal imaging suggests no pathology, study drug administration dosing may continue (with or without dose reduction) with medical monitor approval.

Abbreviations: AEs = adverse events; ALT (SGPT) = alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase); CTCAE = Common Terminology Criteria for Adverse Events; OKA= diabetic ketoacidosis; IV = intravenous; irAE = infusion-related adverse events; TlDM = Type 1 diabetes mellitus

*For patients with liver metastases who begin treatment with Grade 2 AST or ALT, if AST or ALT levels remain grade 2 after study treatment the combination of pembrolizumab/epacadostat may continue at the same dose level without any need to withhold treatment. If AST/ALT resolve to grade 0/1 at any time point following initiation of study treatment and then subsequently increase to grade 2 the guidelines recommended in the section of this table entitled "AST / ALT Elevation or Increased Bilirubin" should be followed.

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

Epacadostat should be permanently discontinued for severe (Grade 4) irAEs. Systemic corticosteroids treatment should be initiated at a dose of 1 to 2 mg/kg per day of prednisone or equivalent for severe irAEs.

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

11.4.2 Pembrolizumab

Dose reductions - Pembrolizumab

Dose reductions of pembrolizumab are not permitted.

Dose Modification (Escalation/Titration/Other)

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per table 16 above.

Other allowed dose interruption for pembrolizumab

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

11.5 Guidelines for the management of specific and immune-related toxicities

Subjects should receive appropriate supportive care measures for immune-related toxicities related to pembrolizumab as deemed necessary by the treating investigator (see Appendix B).

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

Table 17 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 17 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);	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with:

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
prophylactic medications indicated for< =24 hrs	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 mUhr 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.**	Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

11.6 AE and SAE reporting

11.6.1 Time Period and Frequency of Detecting AEs and SAEs

The investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE. See section below for the timeline for reporting SAEs.

AEs and SAEs will be collected from the time the first dose of study treatment is administered until 90 days following discontinuation of study treatment regardless of initiation of a new cancer therapy or transfer to hospice.

After discontinuation of study treatment, the investigator will monitor all AEs/SAEs that are ongoing until resolution or stabilization of the event or until the subject is lost to follow-up. At any time after treatment discontinuation the investigator may report any adverse event that they believe possibly related to study treatment.

11.6.2 Prompt Reporting of Serious Adverse Events and Other Events to MSKCC IRB

Please see section 17.2 for SAE reporting guidelines.

11.6.3 CTCAE term (AE description) and grade

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.03. A copy of the CTCAE version 4.03 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopmenUelectronic_applications/ctc.htm.

11.6.4 Attribution of the AE:

- Definite - The AE is clearly related to the study treatment.
- Probable - The AE is likely related to the study treatment.
- Possible - The AE may be related to the study treatment.
- Unlikely - The AE is doubtfully related to the study treatment.
- Unrelated - The AE is clearly NOT related to the study treatment.

11.7 Pregnancy Testing, Prevention and Lactation Reporting

Epacadostat should not be used by pregnant women. Studies to evaluate the potential for embryotoxicity and teratogenicity have not been performed. Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm.

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

The need for a screening pregnancy test depends on whether a female subject is of childbearing potential or non-childbearing potential.

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

(1) Postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH)

level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

OR

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

OR

Has a congenital or acquired condition that prevents childbearing.

A female of child-bearing potential is defined as any female who does not meet the criteria of non-childbearing potential as described in the previous paragraph.

If a female subject is of childbearing potential, she must have a serum -HCG or urine pregnancy test performed within 72 hours of the first dose of study treatment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Subjects with positive pregnancy test result must be excluded from the study.

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 120 days after the last dose of both epacadostat and pembrolizumab by complying with one of the following:

(1) practice abstinencet from heterosexual activity;

OR

(2) use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are+:

Single method (one of the following is acceptable):

- intrauterine device (IUD)
- vasectomy of a female subject's male partner
- contraceptive rod implanted into the skin

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

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

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

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

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

If a female subject is suspected to be pregnant during the study, a serum pregnancy test must be performed. If pregnancy is confirmed, subject must stop study treatment immediately and the pregnancy must be reported. A report confirming a female subject to be pregnant or lactating has to be reported to Incyte and Merck within 24hours of sponsor awareness and submitted within 10 days of sponsor awareness. The site will contact the pregnant subject at least monthly and document the subject's status until the pregnancy has

been completed or terminated. The outcome of the pregnancy will be reported to the study sponsor and to Merck and Incyte without delay and within 24 hours to the Sponsor and within 2 working days to Merck and Incyte if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor.

11.8 Additional Information Related to Pembrolzumab and Reporting

11.8.1 Definition of a Pembrolizumab Overdose for This Protocol and Reporting of Pembrolizumab Overdose to the Sponsor and to Merck

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. Appropriate supportive treatment should be provided if clinically indicated. In the event of overdose, the subject should be observed closely for signs of toxicity.

If an adverse event[33] is associated with ("results from") the overdose of a Merck product, the adverse event[33] is reported as a serious adverse event, even if no other seriousness criteria are met.

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

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

11.8.2 Events of Clinical Interest

Reporting to Incyte

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

All Serious Adverse Events ("SAE") required to be reported pursuant to the Protocol shall be provided to Incyte and its representatives by Institution or Principal Investigator within twenty-four (24) hours of learning of the event as well as any additional reports agreed upon by Institution or Principal Investigator and Incyte. SAE Reports will be sent to IncytePhVOpsIST@incyte.com. By sending to this e-mail address, the Incyte Pharmacovigilance group will receive copies of the reports. This process will be tested

and established before the first patient is enrolled in the Study. Notwithstanding anything to the contrary herein, Institution will have the primary responsibility of reporting adverse events ("AE") to regulatory authorities.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to Incyte and within 2 working days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Merck product, must be reported within 24 hours to Incyte and within 24 hours to Merck Global Safety.

Events of clinical interest for this trial include:

1. an overdose of Merck product, as defined in Section 11.8.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

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

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

12.1 Antitumor effect

All patients will undergo a baseline staging CT scan of the chest (with or without contrast), abdomen and pelvis (with or without contrast), and MRI of the affected area if deemed necessary by the treating physician. Response evaluations will occur at week 8 and every 8 weeks subsequently (± 1 week window) until week 56, and then less frequently at the discretion of the treating investigator.

Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline, version 1.1 (Primary response criteria).[54] Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

In addition, patients will also be evaluated using the Immune-related Evaluation Response Criteria (irRECIST), which *will not be used* for treatment decisions (Secondary Response Criteria) and are discussed separately in section 12.12

In subjects who have initial evidence of progressive disease (PD) as per RECIST criteria or irRECIST criteria, it is at the discretion of the investigator to continue a subject on study treatment until confirmation of PD 4 weeks. This clinical judgment decision should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data.

Subjects will receive treatment if they are clinically stable as defined by the following criteria:

- Absence of signs and symptoms indicating PD.
- No decline in the Eastern Cooperative Oncology Group (ECOG) performance status
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention

Patients who decide to continue study therapy on protocol after initial radiolgic evidence of disease progression will need to provide written informed consent at the time of the decision to treat beyond initial evidence of progression of disease on study therapy.

12.2 Definitions

Evaluable for toxicity - Patients evaluable for safety analysis will include all patients who have received at least one dose of epacadsotat and pembrolizumab. Patients will be evaluable for toxicity from the time of their first treatment with epacadostat and pembrolizumab.

Evaluable for efficacy - Only those patients who have a measurable disease based on RECIST 1.1 criteria will be eligible for this study, as highlighted in Section 6.0. These patients will have their response classified according to the definitions stated below.

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

be non-responders. Note: one cycle of therapy consists of 21 days where the study therapy (epacadostat and pembrolizumab) is administered at the start of the cycle on day 1)

12.2.1 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 >20mm by chest x-ray, as >10mm with CT scan or MRI, or >10mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

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.

Note: Tumor lesions that are situated in a previously irradiated area are not considered measurable unless there is evidence of progression after radiation therapy.

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

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. 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. The baseline sum diameters will be used as a reference to further characterize any objective 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.

12.3 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 portion of study. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion[33] 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.

12.3.1 Primary Response Criteria (RECIST 1.1)

12.3.1.1 Evaluation of Target Lesions

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 sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease [1]: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

12.3.1.2 Evaluation of Non-Target Lesions

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

Non-CR/Non-PD: Persistence of one or more non-target lesion[33].

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or MSKCC Principal Investigator).

12.3.1.3 Evaluation of Best Response

The best response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Table 18. Evaluation of Best Response - RECIST criteria

Target Lesions	Non-Target Lesions	New Lesions	Best Response	Best Response for This Category also Requires:
CR	CR	No	CR	4 wks. Confirmation
CR	Non-CR/ Non-PD	No	PR	4 wks. Confirmation
PR	Non-CR/ Non-PD	No	PR	
SD	Non-CR/ Non-PD	No	SD	documented at least once 4 wks. from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as ***"symptomatic deterioration."*** Every effort should be made to document the objective progression even after discontinuation of treatment.

12.4 Confirmation of response

Complete or partial response may only be claimed if the criteria for each are met at a subsequent time point (4 weeks later) in studies with a primary endpoint that include response rate.

12.4.1 Special note on target lesions that become "too small to measure"

While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g.

2mm). However, sometimes, lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure". When this occurs, it is important that a value be recorded on the D2M form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as O mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned.

12.5 Not evaluable (NE)

When no imaging/measurement is done at all at a particular time point, the patient is considered not evaluable (NE) at that time point.

12.6 Early death

If the patient has no repeat tumor assessments following initiation of study therapy resulting from the death of the patient due to disease or treatment, it is considered early death.

12.7 Symptomatic Deterioration

Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time be recorded as "symptomatic deterioration". Every effort should be made to document objective progression even after discontinuation of treatment.

12.8 Duration of response

Defined as the time measurement criteria are first met for CR/PR until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurement recorded on study).

12.9 Duration of stable disease

Measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

12.10 Progression-Free Survival (PFS)

PFS is defined as the period from start of study treatment until recurrent or progressive of disease (POD) is objectively documented (taking as reference for progressive disease the smallest measurement recorded on study), death, or date of last study visit involving assessment of disease status.

12.11 Overall Survival (OS)

OS is defined as the observed length of life from start of study treatment to death or the date of last contact.

12.12 Secondary Response Criteria - Immune-related Response Evaluation Criteria in Solid Tumors (irRECIST)

In 2013, Nishina et al. demonstrated that immune-related response criteria using unidimensional measurements were highly concordant with the bidimensional results of irRC, but with less measurement variability.[55] Based on these findings and in order to utilize both the established criteria of irRC and RECIST 1.1, the two systems have been adapted, modified, and combined into the Immune-related Response Evaluation Criteria in Solid Tumors (irRECIST). The adapted irRECIST criteria are modifications to the irRC, incorporating the findings of Nishina et al. and the advantages of RECIST 1.1 while overcoming the shortcomings of each of the other guidelines.

irRECIST
Immune-related RECIST (irRECIST) guidelines according to Bohnsack et al. are presented below.

I. Baseline Assessments in irRECIST

In irRECIST, baseline assessment and measurement of measurable/non-measurable and target/non-target lesions and lymph nodes are in line with RECIST 1.1.

One new definition is added: If a subject has no measurable and no non-measurable disease at baseline the radiologist will assign 'No Disease' (irND) as the overall tumor assessment for any available follow-up time points unless new measurable lesions are identified and contribute to the total measured tumor burden (TMTB). irND is a valid assessment in studies with adjuvant setting where the protocol and study design allow the inclusion of subjects with no visible disease

Follow-up Assessments in irRECIST

A. Follow-up recording of target and new measurable lesions

The key difference in irRECIST is that the appearance of new lesions does not automatically indicate progression. Instead, all measured lesions (baseline-selected target lesions and new measurable lesions) are combined into the total measured tumor burden (TMTB) at follow up. Baseline-selected target lesions and new measurable lesions are

NOT assessed separately. Measurements of those lesions are combined into the TMTB, and one combined assessment provided.

In order to be selected as new measurable lesions (:5 2 lesions per organ, :5 5 lesions total, per time point), new lesions must meet criteria as defined for baseline target lesion selection and meet the same minimum size requirements of 10 mm in long diameter and minimum 15 mm in short axis for new measurable lymph nodes. New measurable lesions should be prioritized according to size, and the largest lesions elected as new measured lesions.

B. Follow-up non-target assessment

RECIST 1.1 definitions for assessment of non-target lesions apply. The response of non-target lesions primarily contributes to the overall response assessments of irCR and irNon-CR/Non-PO (irNN). Non-target lesions do not affect irPR and irSO assessments. Only a massive and unequivocal worsening of non-target lesions alone, even without progress in the TMTB is indicative of irPO. In alignment with RECIST 1.1, baseline selected non-target lesions can never convert to measurable lesions, not even if they increase in size at subsequent time points and become measurable. Only true new lesions can be measured and contribute to the TMTB.

C. Follow-up for New Non-Measurable Lesions

All new lesions not selected as new measurable lesions are considered new non-measurable lesions and are followed qualitatively. Only a massive and unequivocal progression of new non-measurable lesions leads to an overall assessment of irPO for the time point. Persisting new non-measurable lesions prevent irCR.

Overall Assessments for irRECIST

The irRECIST overall tumor assessment is based on TMTB of measured target and new lesions, non-target lesion assessment and new non-measurable lesions.

At baseline, the sum of the longest diameters (SumO) of all target lesions (up to 2 lesions per organ, up to total 5 lesions) is measured. At each subsequent tumor assessment (TA), the Sumo At each subsequent tumor assessment (TA), the Sumo of the target lesions and of new, measurable lesions (up to 2 new lesions per organ, total 5 new lesions) are added together to provide the total measurable tumor burden (TMTB). In the setting where treatment is continued beyond progression further assessments using irRECIST will use the first scan showing progressive disease as the new baseline scan to which all subsequent scans are compared.

Table 18. Overall Assessment by irRECIST

Complete Response (irCR)	Complete disappearance of all measurable and non-measurable lesions. Lymph nodes must decrease to < 10 mm in short axis.
Partial Response (irPR)	Decrease of 30% in TMTB relative to baseline, non-target lesions are irNN, and no unequivocal progression of new non-measurable lesions • If new measurable lesions appear in subjects with **no target lesions at baseline,** irPD will be assessed. That irPD time point will be considered a new baseline, and all subsequent time points will be compared to it for response assessment. irPR is possible if the TMTB of new measurable lesions decreases by 30% compared to the first irPD documentation • irRECIST can be used in the **adjuvant setting,** in subjects with no visible disease on CT/MRI scans. The appearance of new measurable lesion(s) automatically leads to an increase in TMTB by 100% and leads to irPD. These subjects can achieve a response if the TMTB decreases at follow-up, as a sign of delayed response. • Based on the above, sponsors may consider enrolling subjects with no measurable disease and/or no visible disease in studies with response related endpoints.
Stable Disease (irSD)	Failure to meet criteria for irCR or irPR in the absence of irPD
Progressive Disease (irPD)	Minimum 20% increase and minimum 5 mm absolute increase in TMTB compared to nadir, or irPD for non-target or new non-measurable lesions. Confirmation of progression is recommended minimum 4 weeks after the first

	irPD assessment. An irPD confirmation scan may be recommended for subjects with a minimal TMTB %-increase over 20% and especially during the flare time-window of the first 12 weeks of treatment, depending on the compound efficacy expectations, to account for expected delayed response. • In irRECIST a substantial and unequivocal increase of **non-target lesions** is indicative of progression. • IrPD may be assigned for a subject with multiple **new non-measurable lesions** if they are considered to be a sign of unequivocal massive worsening
Other	**irNE:** used in exceptional cases where insufficient data exist. **irND:** in adjuvant setting when no disease is detected **irNN:,** no target disease was identified at baseline, and at follow-up the subject fails to meet criteria for irCR or irPD

13.0 CRITERIA FOR REMOVAL FROM STUDY

Patients will be removed from the study when any of the criteria listed below applies. The reason for removal from the study and the date the patient was removed must be documented in the Clinical Research Database system. Patients who come off study before their first radiological assessment from baseline for reasons other than disease progression or treatment related toxicities may be replaced.

All patients who have received at least one dose of both study treatments will be assessable for safety of the combination therapy. Patients evaluable for efficacy analysis will include all patients who have received at least one cycle of treatment with both epacadostat and pembrolizumab and assessable for response. Patients who are missing an assessment of response post baseline will not be considered evaluable for response unless they missed

the assessment due to progression of disease or treatment related toxicities in which case they will be considered non-responders for that time point.

In the absence of treatment delays due to adverse events, treatment with epacadostat and/or pembrolizumab may continue until one of the following criteria applies:

- Intercurrent illness that prevents further administration of treatment
- Intolerance of study treatment
- Patient decides to withdraw from the study
- Physician decides to withdraw a patient from the study for a reason not listed here
- Pregnancy in patient
- The patient is lost to follow-up
- Inability of the patient to comply with the requirement of the protocol for treatment or evaluation.
- End of study, whichever occurs first.

Due to the mechanism of action, subjects may experience growth in existing tumors or the appearance of new tumors prior to maximal clinical benefit of epacadostat and pembrolizumab. The patient may be allowed to continue study treatment after initial RECIST 1.1 defined progression if they are assessed by the treating physician to be deriving clinical benefit and tolerating study treatment. The treating physician may consult with the overall study PI for help with assessing the patient. Such patients should discontinue study therapy upon further evidence of progression at the discretion of the treating investigator.

Safety follows up and End of Study visit

Upon permanent discontinuation from the study treatment for any reason, the following procedures will be performed approximately 30 (+7) days after the last dose of epacadostat or the last dose of pembrolizumab, whichever is later.

Full medical history, physical exam, assessment of performance status by KPS or ECOG status

Review of concomitant medications

Complete vital signs (pulse, blood pressure, temperature, respiratory rate, oxygen saturation) as well as weight and height. Height may be documented at any time prior to registration.

12-lead electrocardiogram (ECG)

Serum -HCG or urine pregnancy test for women with child-bearing potential. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

Complete blood count with differential, including lymphocyte and eosinophil count.

Comprehensive metabolic panel (glucose, blood urea nitrogen, creatinine, sodium, potassium, chloride, bicarbonate, calcium, total protein, albumin, serum bilirubin, alkaline phosphatase, ASL, AST)
phosphorus, magnesium

TSH, T4 free, T3

Amylase and lipase

An optional biopsy will be offered at progression of disease.

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value must be followed until resolution or stabilization of the event.

Reporting of adverse events will occur for up to 90 days for serious adverse events (within 90 [+7] days after the last administration of epacadostat or pembrolizumab, whichever is later), Events of Clinical Interest (within 90 [+7] days after the last administration of epacadostat or pembrolizumab, whichever is later), and documentation of concomitant medications.

Long-Term Follow-up Procedures:

All subjects who permanently discontinue study drug for any reason other than withdrawal of full consent will be contacted by clinic visit or telephone to assess survival and initiation of additional sarcoma therapy. Contact for all subjects will be attempted every 12 weeks (±28 days) following the safety follow-up visit until death, subject withdraws full consent, or up to 12 months after the end of treatment.

14.0 BIOSTATISTICS

14.1 Primary Endpoint

The primary objective is to evaluate the efficacy, as assessed by the best objective response rate (complete response + partial response) by 24 weeks by RECIST 1.1. The study will use a one stage design based on the exact binomial test. A 10% response rate will be considered not promising; a 30% response rate will be considered promising.There will be a maximum accrual of 30 patients to this study. It will be concluded that the true response rate is > 10% if there are 6 or more patients with an objective response among 30 patients. The design has a type I error rate of 0.07 and a type II error rate of 0.08. This design provides 92% probability of a positive result if the true response rate is at least 30%, and a 93% probability of a negative result if the true response rate is 10% or lower.

The patient population in this study represents patients with locally advanced/metastatic sarcoma that have received at least one line of previous therapy. The data supporting the 10% null rate comes from the SARC028 study that evaluated the efficacy of pembrolizumab monotherapy among patients with advanced/metastatic sarcoma which is discussed further below. In assessing the efficacy of a combination therapy incorporating pembrolizumab in this study population a response rate of> 10% would be preferred to determine the therapy as having a signal of efficacy.
Patients evaluable for efficacy analysis will include all patients who have received at least one cycle of treatment with epacadostat and pembrolizumab and are assessable for response. Patients who are missing an assessment of response post baseline will not be considered evaluable for response unless they missed the assessment due to progression of disease or treatment related toxicities in which case they will be considered non-responders for that time point. Patients who miss an assessment of response post baseline for any reason other than progression of disease and treatment related toxicity will be replaced.

Are knowledge regarding the efficacy of immunotherapy in sarcoma is evolving. As previously outlined, two studies evaluating the role of anti-PD1 monotherapy in patients with sarcoma were presented at the ASCO annual meeting in 2016. One study confirmed that no responses were seen among 12 patients with uterine LMS treated with nivolumab.[21] The second study evaluated pembrolizumab in bone and soft tissue sarcomas (SARC028).[20] Signals of efficacy were observed in patients with UPS, liposarcoma (poorly differentiated/defferentiated) and chondrosarcoma. The objective response rates observed in this study was 19% for soft tissue sarcoma and was 5% for bone sarcoma. The objective response rates observed in this study for specific histologic subtypes were as follows: UPS -44%; liposarcoma -22%; synovial sarcoma 11%; leiomyosarcoma - 0%; chondrosarcoma - 17%; ewing's sarcoma - 0%; osteosarcoma - 5%. In relation to this trial design, patients with sarcoma subtypes where limited benefit from anti-PD1 monotherapy was observed in

previous studies may benefit from the combination immunotherapy approach offered in this study. Therefore, patients will be accrued based on histological sarcoma subtype into one of 4 cohorts. This will ensure that we enroll patients with an adequate spead of sarcoma histologies. Each cohort will enroll a prespecified number of patients with specific sarcoma histological subtypes. Due to the small sample size in each cohort, a sufficiently-powered efficacy analysis for each cohort is not possible however, the objective response rate for i) soft tissue sarcomas ii) bone sarcomas (if applicable depending on enrolment), and iii) within each cohort +/ each histological sarcoma subtype will be examined to look for a potential signal of efficacy.

We expect to accrue approximately 1-2 patients each month and hence expect to finish enrollment in 15-20 months.
The anticipated accrual rate for each cohort is as follows:

A) Undifferentiated Pleomorphic Sarcoma (UPS)/ Liposarcoma (dedifferentiated or pleomorphic liposarcoma) - one patient every month

B) Leiomyosarcoma - one patient every second month

C) Vascular Sarcoma Subtypes (including angiosarcoma, Epithelioid Hemangioendothelioma (EHE),)- one patient every 3-4 months

D) Other - one patient every second month

14.2 Secondary Endpoints

Secondary endpoints include:
1. Safety
Patients evaluable for safety analysis will include all patients who have received at least one dose of epacadsotat and pembrolizumab. Adverse events will be graded according to the NCI CTCAE v4.03, presented on an individual basis and summarized using descriptive statistics.

2. Survival
Progression free survival (PFS) rate at 24 weeks, median PFS, overall survival (OS) and progression-free survival intervals will be estimated using Kaplan-Meier methodology

3. Best Objective Response Rate by irRECIST
Best objective response rate (complete response + partial response) by 24 weeks by immune-related response criteria (irRECIST), of epacadostat in combination with pembrolizumab in patients with metastatic and/or locally advanced, sarcoma.

14.3 Correlative Endpoints Statistical Considerations

The study is not powered to detect specific hypotheses. Due to the small sample size, the correlative studies will be exploratory and hypothesis generating in nature. These analyses will help better identify patients having the potential to benefit from this therapy and aid in designing larger phase III studies.

I. To evaluate the baseline characteristics of sarcoma tumors (pre-treatment biopsy sample) evaluated in this study including the level of 1001, kynurenine and PD-1/PD-L1 expression, presence of tumor infiltrating lymphocytes (TILs) and tumor antigens, gene expression profile, and the T-cell receptor clonality in tumor-infiltrating lymphocytes (TIL). Descriptive statistics will be used to report the baseline tumor characteristics with respect the level of 1001, kynurenine and PD-1/PD-L1 expression, presence of tumor infiltrating lymphocytes (TIls) and tumor antigens, gene expression profile, and the T-cell receptor clonality in tumor-infiltrating lymphocytes (TIL).

II. To assess the potential effect of epacadostat and pembrolizumab on selected biomarker expression measured in pre- and post-treatment tumor tissue and the association between these biomarkers and with clinical outcome, including characterization of 100-1, PD-1/PD-L1, kynurenine expression, tumor infiltrating lymphocytes (TIls) and tumor antigens, gene expression profiling, and characterization of T-cell receptor clonality in tumor-infiltrating lymphocytes (TIL). The pre- and post-treatment measurements will be compared using the paired t-test for each of these biomarkers. The associations with the selected biomarkers, in terms of both the pre-treatment measurement and the difference between pre- and post-treatment measurements, will be evaluated using the two-sample t-test for clinical outcome such as response and clinical benefit, and using survival data analysis (including Kaplan-Meier curve and Cox Proportional Hazards models) for survival outcomes such as progression-free survival and survival. More specifically, Kaplan-Meier curve and Cox Proportional Hazards models will be used for analyzing pre-treatment measurement; Kaplan-Meier curve at a landmark time point and Cox Proportional Hazards models allowing for time varying coefficients will be used for analyzing the difference between pre-and post treatment measurements.

III. To evaluate associations between selected biomarkers measured in serial peripheral blood over time with clinical efficacy, including immunophenotyping and functional analyses, evaluation of serum levels of chemokines, cytokines and other immune mediators, and characterization of T-cell receptor clonality in peripheral blood.

Summary statistics will be used to for describing changes across time. In addition the time course of biomarker measurements will be investigated graphically, by summary plots or individual patient plots; their trends over time will be categorized either by visual inspection (if there are clear trend groups such as monotonically increasing or

monotonically decreasing) or by pattern recognition methods such as K-means clustering. The associations with the observed trend in selected biomarkers analyzed will be evaluated using categorical data analysis (including Fisher's exact test and logistic regression) for clinical outcome such as response and clinical benefit, and using survival data analysis (including Kaplan-Meier curve and Cox Proportional Hazards models) for survival outcomes such as progression-free survival and survival.

IV. To evaluate the association between baseline tumor mutational burden and neoantigen production with clinical efficacy of the study therapy.

The associations with baseline tumor mutational burden and neoantigen production will be evaluated using categorical data analysis (including Fisher's exact test and logistic regression) for clinical outcome such as response and clinical benefit, and using survival data analysis (including Kaplan-Meier curve and Cox Proportional Hazards models) for survival outcomes such as progression-free survival and survival.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

15.2 Randomization

N/A

16.0 DATA MANAGEMENT ISSUES

A Clinical research coordinator (CRC) will be assigned to the study. The responsibilities of the CRC include project compliance, data collection, abstraction and entry, data reporting,

regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team.

The data collected for this study will be entered into a secure database. Source documentation will be available to support the computerized patient record.

16.0.1 Data

16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: http://mskweb5.mskcc.org/intranet/html/99074.cfm

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: Data and Safety Monitoring Committee (DSMC) for Phase I and II clinical trials, and the Data and Safety Monitoring Board (DSMB) for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g.,

NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) Will be addressed and the monitoring procedures will be established at the time of protocol activation

Final data sets for publication are required to be locked and stored centrally for potential future access requests from outside entities.

16.3 Regulatory Documentation

Prior to implementing this protocol at MSKCC, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MSKCC Institutional Review Board/Privacy Board (IRB/PB). There will be one protocol document and each participating site will utilize that document.

Participating sites that are conducting data analysis should submit this protocol to their IRB according to local guidelines. Copies of any site IRB correspondence should be forwarded to MSK.

Role of Stanford University as the participating site is as follows:

Data analysis being performed by the site: Diagnosis, Age, Gender, ECOG, Prior therapies, All efficacy response parameters (ORR, DOR, PFS, OS) will be shared with Stanford

The data will be shared via secure file transfer system

The data will be shared at the end of the study

Participant identifiers will not be shared

Role of MD Anderson Cancer Center as the participating site is as follows:

Data analysis being performed by the site: Computational analysis of any tumor sequencing available and combining it with sequencing data available through MD Anderson cohorts. Also, genomic correlates of response to immunotherapy, histology-specific determinants of response to ICB
Data will be shared via Secure File Transfer System
Data will be shared as soon as possible since the study has been completed.
Participant identifiers will not be shared. Only clinical data and demographics will be shared.

16.3.1 Amendments

Each change to the protocol document must be organized and documented by MSKCC and approved by the MSKCC IRB/PB.

Prospective and Retrospective deviations

A protocol deviation on this study is defined as a request to treat a research participant who does not meet all the eligibility criteria, pretreatment evaluation, or who requires alteration in their study plan. If a deviation from this protocol is proposed for a potential or existing participant at MSKCC, approval from the MSKCC IRB/PB is required prior to the action. A protocol violation is anything that occurs with a participant, which deviated from the protocol without prior approval from the MSKCC IRB/PB. The MSKCC **PI** will in turn report the violation to the MSKCC IRB/PB.

16.3.3 Document maintenance

The MSKCC **PI** will maintain adequate and accurate records to enable the implementation of the protocol to be fully documented and the data to be subsequently verified.

17.0 PROTECTION OF HUMAN SUBJECTS

Participation in this trial is voluntary. The patients will be explained e extent of the risks, benefits, toxicities/side effects, alternatives/options for treatment, financial costs/burdens, and the voluntary nature of the study. All patients will be required to sign a statement of informed consent, which must conform to Institutional Review Board guidelines.

Inclusion of Women and Minorities: Memorial Sloan Kettering Cancer Center has filed forms: HHS 441 (civil rights), HHS (handicapped individual), 639-A (sex discrimination), and 680 (age discrimination); we also take due notice of the NIH policy concerning inclusion of women and minorities in clinical research populations. Patients of all races, both male and female, will be accepted into the protocol. The proposed study population is as described in section 6.0.

Exclusion of Lactating or Pregnant Women: Lactating and pregnant women are also excluded because of unknown effects of epacadostat and/or pembrolizumab that may be harmful to the developing fetus or nursing infant.

Inclusion of Children in Research: The protocol/project does not include patients younger than the age of 18. Although sarcomas are the most common solid tumor in children, pediatric sarcomas are treated with specific protocols.

Benefits: It is possible that this treatment will result in shrinkage of the tumor or in a stabilization of an otherwise progressing disease. It is not known, of course, whether these or any other favorable events will occur. It is not known whether this treatment will affect the overall survival of the patients.

Costs: The patient will be responsible for the costs of standard medical care, including all drug administration fees and all hospitalizations, even for complications charge.

Research-only biopsies and laboratory tests will no be charged to the patient. Research testing on tissue will not be charged to the patient.

Incentives: No incentives will be offered to the patients/subjects for participation in the study.

Alternatives: For patients with locally advanced and/or metastatic sarcomas alternative treatments may include conventional cytotoxic chemotherapies including, but not limited to: doxorubicin, ifosfamide, gemcitabine in combination with docetaxel, liposomal doxorubicin, dacarbazine, temozolomide, vinorelbine; and also tyrosine kinase inhibitors depending on the histology, including, but not limited to: imatinib, sorafenib, sunitinib, pazopanib. Epacadostat and pembrolizumab are not yet approved by the Food and Drug Administration, but may be part of the treatment in a different clinical trial.

Confidentiality: Every effort will be made to maintain the patient confidentiality. Research and hospital records are confidential. Patient's name or any other personally identifying information will not be used in reports or publications resulting from this study. The Food and Drug Administration or other authorized agencies (e.g., qualified monitors from MSKCC or collaborating institutions) may review patients' records and pathology slides, as required.

17.1 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers, and members of the research teams at participating sites who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with other qualified researchers.

The consent indicates that samples and genetic information collected may be shared with other qualified researchers and placed in online databases. An example of an online database is the NIH dbGAP database, which is monitored by the National Institutes of Health, and may be made accessible to investigators approved by the U.S. government. Such information will not include identifying information such as name. It is also stated in the Research Authorization that research data (e.g. genomic sequence) may be shared with regulators. The requirements for submission of genotype/phenotype data into the NIH dbGAP or any other public database will be followed as per the IRB SOP for Genomic Data Sharing.

17.2 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

• Death

• A life-threatening adverse event

• An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization

• A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

• A congenital anomaly/birth defect

• Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.
SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

The date the adverse event occurred

• The adverse event

• The grade of the event

• Relationship of the adverse event to the treatment(s)

• If the AE was expected

• Detailed text that includes the following

  o An explanation of how the AE was handled

  o A description of the participant's condition

  o Indication if the participant remains on the study

• If an amendment will need to be made to the protocol and/or consent form

• If the SAE is an Unanticipated Problem

The SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the IND Office

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

18.0 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 IRS/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.

19.0 REFERENCES

1. Lindberg RD, Martin RG, Romsdahl MM, Barkley HT, Jr. Conservative surgery and postoperative radiotherapy in 300 adults with soft-tissue sarcomas. Cancer 1981;47:2391-7.
2. Weitz J, Antonescu CR, Brennan MF. Localized extremity soft tissue sarcoma: improved knowledge with unchanged survival over time. J Clin Oncol 2003;21:2719-25.
3. Billingsley KG, Burt ME, Jara E, et al. Pulmonary metastases from soft tissue sarcoma: analysis of patterns of diseases and postmetastasis survival. Ann Surg 1999;229:602-10; discussion 10-2.
4. Van Glabbeke M, van Oosterom AT, Oosterhuis JW, et al. Prognostic factors for the outcome of chemotherapy in advanced soft tissue sarcoma: an analysis of 2,185 patients treated with anthracycline-containing first-line regimens--a European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Study. J Clin Oncol 1999;17:150-7.
5. Brennan MF. Management of Soft Tissue Sarcoma. New York: Springer; 2003.
6. Coley WB. II. Contribution to the Knowledge of Sarcoma. Ann Surg 1891;14:199-220.
7. Gatti RA, Good RA. Occurrence of malignancy in immunodeficiency diseases. A literature review. Cancer 1971;28:89-98.
8. Sorbye SW, Kilvaer T, Valkov A, et al. Prognostic impact of lymphocytes in soft tissue sarcomas. PLoS One 2011;6:e14611.

9. Berghuis D, Santos SJ, Baelde HJ, et al. Pro-inflammatory chemokine-chemokine receptor interactions within the Ewing sarcoma microenvironment determine CDS(+) T-lymphocyte infiltration and affect tumour progression. J Pathol 2011;223:347-57.
10. Zhang L, Conejo-Garcia JR, Katsaros D, et al. Intratumoral T cells, recurrence, and survival in epithelial ovarian cancer. N Engl J Med 2003;348:203-13.
11. Balachandran VP, Cavnar MJ, Zeng S, et al. Imatinib potentiates antitumor T cell responses in gastrointestinal stromal tumor through the inhibition of Ido. Nat Med 2011;17:1094-100.
12. Brinkrolf P, Landmeier S, Altvater B, et al. A high proportion of bone marrow T cells with regulatory phenotype (CD4+CD25hiFoxP3+) in Ewing sarcoma patients is associated with metastatic disease. Int J Cancer 2009;125:879-86.
13. Nakayama T, Tsuboyama T, Toguchida J, Hosaka T, Nakamura T. Natural course of desmoid-type fibromatosis. J Orthop Sci 2008;13:51-5.
14. Chou AJ, Kleinerman ES, Krailo MD, et al. Addition of muramyl tripeptide to chemotherapy for patients with newly diagnosed metastatic osteosarcoma: a report from the Children's Oncology Group. Cancer 2009;115:5339-48.
15. Edmonson JH, Long HJ, Creagan ET, Frytak S, Sherwin SA, Chang MN. Phase II study of recombinant gamma-interferon in patients with advanced nonosseous sarcomas. Cancer Treat Rep 1987;71:211-3.
16. Edmonson JH, Long HJ, Frytak S, Smithson WA, Itri LM. Phase II study of recombinant alfa-2a interferon in patients with advanced bone sarcomas. Cancer Treat Rep 1987;71:747-8.
17. Ito H, Murakami K, Yanagawa T, et al. Effect of human leukocyte interferon on the metastatic lung tumor of osteosarcoma: case reports. Cancer 1980;46:1562-5.
18. Schwinger W, Klass V, Benesch M, et al. Feasibility of high-dose interleukin-2 in heavily pretreated pediatric cancer patients. Ann Oncol 2005;16:1199-206.
19. Robbins PF, Morgan RA, Feldman SA, et al. Tumor regression in patients with metastatic synovial cell sarcoma and melanoma using genetically engineered lymphocytes reactive with NY-ESO-1. J Clin Oncol 2011;29:917-24.
20. Tawbi HA-H, Burgess MA, Crowley J, et al. Safety and efficacy of PD-1 blockade using pembrolizumab in patients with advanced soft tissue (STS) and bone sarcomas (BS): Results of SARC028--A multicenter phase II study. ASCO Meeting Abstracts 2016;34:11006.
21. Ben-Ami E, Barysauskas CM, Solomon S, et al. Immunotherapy with single agent nivolumab for advanced leiomyosarcoma of the uterus: Results of a phase 2 study. Cancer 2017.
22. Sharma A, Bode B, Studer G, et al. Radiotherapy of human sarcoma promotes an intratumoral immune effector signature. Clin Cancer Res 2013;19:4843-53.
23. Uyttenhove C, Pilotte L, Theate I, et al. Evidence for a tumoral immune resistance mechanism based on tryptophan degradation by indoleamine 2,3-dioxygenase. Nat Med 2003;9:1269-74.
24. Spranger S, Spaapen RM, Zha Y, et al. Up-regulation of PD-L1, IDO, and T(regs) in the melanoma tumor microenvironment is driven by CDS(+) T cells. Sci Transl Med 2013;5:200ra116.
25. Baban B, Chandler PR, Sharma MD, et al. IDO activates regulatory T cells and blocks their conversion into Th17-like T cells. J Immunol 2009;183:2475-83.
26. Vanderstraeten A, Luyten C, Verbist G, Tuyaerts S, Amant F. Mapping the immunosuppressive environment in uterine tumors: implications for immunotherapy. Cancer Immunol Immunother 2014;63:545-57.
27. Toulmonde M, Adam J, Bessede A, et al. Integrative assessment of expression and prognostic value of POL1, IDO, and kynurenine in 371 primary soft tissue sarcomas with genomic complexity. ASCO Meeting Abstracts 2016;34:11008.
28. Urakawa H, Nishida Y, Nakashima H, Shimoyama Y, Nakamura S, Ishiguro N. Prognostic value of indoleamine 2,3-dioxygenase expression in high grade osteosarcoma. Clin Exp Metastasis 2009;26:1005-12.

29. Max D, Kuhnol CD, Burdach S, Niu L, Staege MS, Foll JL. Indoleamine-2,3-dioxygenase in an immunotherapy model for Ewing sarcoma. Anticancer Res 2014;34:6431-41.
30. Galon J, Costes A, Sanchez-Cabo F, et al. Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. Science 2006;313: 1960-4.
31. Liu X, Newton RC, Friedman SM, Scherle PA. Indoleamine 2,3-dioxygenase, an emerging target for anti-cancer therapy. Curr Cancer Drug Targets 2009;9:938-52.
32. Patnaik A, Kang SP, Rasco D, et al. Phase I Study of Pembrolizumab (MK-3475; Anti-PD-1 Monoclonal Antibody) in Patients with Advanced Solid Tumors. Clin Cancer Res 2015;21:4286-93.
33. Robert C, Ribas A, Wolchok JD, et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. Lancet (London, England) 2014;384:1109-17.
34. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. The New England journal of medicine 2015;372:2521-32.
35. Hamid 0, Robert C, Daud A, et al. Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. N Engl J Med 2013;369:134-44.
36. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. The New England journal of medicine 2016;375:1823-33.
37. Seiwert TY, Burtness B, Mehra R, et al. Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial. The Lancet Oncology 2016;17:956-65.
38. Ribas A, Puzanov I, Dummer R, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. The Lancet Oncology 2015;16:908-18.
39. Herbst RS, Baas P, Kim OW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet (London, England) 2016;387:1540-50.
40. Mehra R ST, Mahipal A, et al. Efficacy and safety of pembrolizumab in recurrenUmetastatic head and neck squamous cell carcinoma (R/M HNSCC): Pooled analyses after long-term follow-up in KEYNOTE-012. ASCO annual meeting; 2016.
41. Daud A BC, Robert C et al. . KEYNOTE-006 study of pembrolizumab (pembro) versus ipilimumab (ipi) for advanced melanoma: Efficacy by PD-L1 expression and line of therapy.. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2016;34.
42. Daud Al, Wolchok JD, Robert C, et al. Programmed Death-Ligand 1 Expression and Response to the Anti-Programmed Death 1 Antibody Pembrolizumab in Melanoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2016;34:4102-9.
43. Merelli B, Massi D, Cattaneo L, Mandala M. Targeting the PD1/PD-L1 axis in melanoma: biological rationale, clinical challenges and opportunities. Crit Rev Oncol Hematol 2014;89:140-65.
44. van Rooij N, van Buuren MM, Philips D, et al. Tumor exome analysis reveals neoantigen-specific T-cell reactivity in an ipilimumab-responsive melanoma. J Clin Oncol 2013;31:e439-42.
45. Lundegaard C, Lamberth K, Harndahl M, Buus S, Lund 0, Nielsen M. NetMHC-3.0: accurate web accessible predictions of human, mouse and monkey MHC class I affinities for peptides of length 8-11. Nucleic Acids Res 2008;36:W509-12.
46. Matsushita H, Vesely MD, Koboldt DC, et al. Cancer exome analysis reveals a T-cell-dependent mechanism of cancer immunoediting. Nature 2012;482:400-4.
47. DuPage M, Mazumdar C, Schmidt LM, Cheung AF, Jacks T. Expression of tumour-specific antigens underlies cancer immunoediting. Nature 2012;482:405-9.
48. Snyder A, Makarov V, Merghoub T, et al. Genetic basis for clinical response to CTLA-4 blockade in melanoma. N Engl J Med 2014;371:2189-99.
49. Maki RG, Jungbluth AA, Gnjatic S, et al. A Pilot Study of Anti-CTLA4 Antibody Ipilimumab in Patients with Synovial Sarcoma. Sarcoma 2013;2013:168145.

50. Gangadhar TC, Hamid, 0, Smith, D.C, . Epacadostat plus pembrolizumab in patients with advanced melanoma and select solid tumors: Updated phase 1 results from ECHO-202/KEYNOTE-037 ESMO; 2016.
51. Gangadhar TC H, 0, Smith, D.C. Epacadostat plus pembrolizumab in patients with advanced melanoma and select solid tumors: Updated phase 1 results from ECHO-202/KEYNOTE-037. ESMO; 2016.
52. Heinrich MC, Corless CL, Demetri GD, et al. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. J Clin Oncol 2003;21:4342-9.
53. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012;366:2443-54.
54. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.
55. Nishino M, Giobbie-Hurder A, Gargano M, Suda M, Ramaiya NH, Hodi FS. Developing a common language for tumor response to immunotherapy: immune-related response criteria using unidimensional measurements. Clinical cancer research : an official journal of the American Association for Cancer Research 2013;19:3936-43.

20.0 APPENDICES

List appendices here. Appendices will be stored in a separate file and will be submitted in electronic and/or paper format. If electronic format, please submit on file per appendix.

Appendix A. Procedure for Research Blood and Biopsy Collection

Research Biopsy Collection

Given the requirement for fresh and frozen tissue, FFPE archival samples cannot be substituted for the baseline or subsequent biopsies.

The same metastatic tumor site should be biopsied at each time point if feasible. Cores will be representative of tumor and obtained with 18-gauge needles where appropriate and be of at least 1cm in length. Cores will be representative of tumor, and targeted to the de-differentiated component in the case of de-differentiated liposarcoma.

The quality, viability and tumor content of biopsies will be confirmed by the on-call clinical pathologist at the time of retrieval.

A goal of 6 cores should be obtained with a minimum of one formalin-fixed, one fresh and one flash frozen in liquid nitrogen.

1 FFPE (path core)

2 Fresh (Immune monitoring facility (IMF))

3 Flash frozen (IMF)

4 Fresh (IMF)

5 Flash frozen (IMF)

6 FFPE (path core)

FFPE cores should be placed in formaldehyde solution and sent to the central pathology lab.

Fresh core should be placed in RPMI media in a falcon tube and transported on ice (RPMI media should be kept in a fridge and should not be kept longer than two weeks, fresh bottle are available from the IMF lab)

Flash frozen cores should be placed in a clean cryovial (nunc tube) then placed in liquid nitrogen for at least 2 minutes, transported in preferably a dewar flask of liquid nitrogen or in dry ice.

If any extra cores are obtained they should be flash frozen with liquid nitrogen as above.

Samples will be labeled using an adherent, liquid nitrogen proof label with the following information:

1) Procurement date
2) Study IRB number
3) Study patient number
4) Time point (baseline or on-treatment)
5) Anatomical biopsy site

Research blood collection

Please schedule research blood draws for the morning and have them batched and sent to the lab by 2pm (they can take up to 2 hours to be delivered by STAT messenger) Bloods cannot be processed on the same day if they arrive after 4pm.

At each research blood collection time point the following samples will be collected:

4x8ml of peripheral venous blood will be collected in green/red speckled top CPT vacutainer tubes. The tubes will be inverted 8-10 times to mix the sodium heparin solution. Specimens will be placed in a biohazard bag and kept at room temperature.

Samples will be labeled with the following information:

1) Procurement date
2) Study IRB number
3) Study patient number
4) Time point (baseline or week-X)

Laboratory Contact Details

Research blood samples and tumor biopsy samples, along with completed requisition forms, are to be transported to the Immune Monitoring Facility in the Zuckerman Research Bldg, Room Z-1513. At least 24 hr advanced notification prior to biopsy or blood collection must be provided by email to the IMF contacts below or entered in the IMF shared calendar (zzCAL_LAB_Clinical_Trials/Shared Calendar), with clinical site location and contact information from which samples are arriving indicated. Samples must be delivered between the hours of 9 am-4 pm to a member of the lab.

Rosemarie Ramsawak <ramsawar@mskcc.org> 646-888-3106

Zhenyu Mu <muz@mskcc.org> 646-888-2114

Kevin Crawford <crawfork@mskcc.org> 646-888-3106

Luisa Caro <carol@mskcc.org> 646-888-3106

Appendix B.

Supportive care guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

A2.1 Pneumonitis

All attempts should be made to rule out other causes such as metastatic disease, bacterial or viral infection. It is important that patients with a suspected diagnosis of pneumonitis be managed as per the guidance below until treatment-related pneumonitis is excluded. Treatment of both a potential infectious etiology and pneumonitis in parallel may be

warranted. Management of the treatment of suspected pneumonitis with steroid treatment should not be delayed for a therapeutic trial of antibiotics.

If an alternative diagnosis is established, the patient does not require management as below.

Course of Action

Grade 2 events:

- Hold pembrolizumab.
- Consider pulmonary consultation with bronchoscopy and biopsy/BAL.
- Consider ID consult
- Conduct an in person evaluation approximately twice per week
- Consider frequent Chest X-ray as part of monitoring
- Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- Second episode of pneumonitis - discontinue pembrolizumab if upon re-challenge the patient develops a second episode of Grade 2 or higher pneumonitis.

Grade 3 and 4 events:

- Discontinue pembrolizumab.
- Hospitalize patient
- Bronchoscopy with biopsy and/or BAL is recommended.
- Immediately treat with intravenous steroids (methylprednisolone 125 mg IV). When symptoms improve to Grade 1 or less, a high dose oral steroid (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours) taper should be started and continued over no less than 4 weeks.
- If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, treat with additional anti-inflammatory measures. Discontinue additional antiinflammatory measures upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days. If symptoms worsen during steroid reduction, initiate a re-tapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer additional antiinflammatory measures, as needed
- Add prophylactic antibiotics for opportunistic infections.

A2.2 Colitis

All attempts should be made to rule out other causes such as metastatic disease, bacterial or parasitic infection, viral gastroenteritis, or the first manifestation of an inflammatory bowel

disease by examination for stool leukocytes, stool cultures, a Clostridium difficile titer and endoscopy.

Course of Action

Grade 2 Diarrhea/Colitis (4-6 stools/day over baseline, dehydration requiring IV fluids< 24 hours, abdominal pain, mucus or blood in stool):

- Hold pembrolizumab.
- Symptomatic Treatment
- For Grade 2 diarrhea that persists >1 week, and for diarrhea with blood and/or mucus,
    - Consider GI consultation and endoscopy to confirm or rule out colitis
    - Administer oral corticosteroids (prednisone 1-2 mg/kg QD or equivalent)
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- If symptoms worsen or persist > 3 days treat as Grade 3

Grade 3 Diarrhea/Colitis (or Grade 2 diarrhea that persist for greater than 3 days):

- Hold pembrolizumab.
- Rule out bowel perforation. Imaging with plain films or CT can be useful.
- Recommend consultation with Gastroenterologist and confirmation biopsy with endoscopy.
- Treat with intravenous steroids (methylprednisolone 125 mg) followed by high dose oral steroids (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours) When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Taper over 6 to 8 weeks in patients with diffuse and severe ulceration and/or bleeding.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, consider treatment with additional anti-inflammatory measures as described in the literature. Discontinue additional anti-inflammatory measures upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days. If symptoms worsen during steroid reduction, initiate a re-tapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer additional anti-inflammatory measures as needed.

Grade 4 events:

- Permanently discontinue pembrolizumab.
- Manage as per Grade 3.

A2.3 Endocrine

All attempts should be made to rule out other causes such as brain metastases, sepsis and/or infection.

Hypophysitis or other symptomatic endocrinopathy other than hypo- or hyperthyroidism

Grade 2 events:

- Hold pembrolizumab
- Monitor thyroid function or other hormonal level tests and serum chemistries more frequently until returned to baseline values.
- Pituitary gland imaging should be considered (MRIs with gadolinium and selective cuts of the pituitary can show enlargement or heterogeneity and confirm the diagnosis).
- Treat with prednisone 40 mg p.o. or equivalent per day. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- Consultation with an endocrinologist may be considered.

Grade 3 events:

- Hold pembrolizumab.
- Endocrine consultation is recommended.
- Rule out infection and sepsis with appropriate cultures and imaging.
- Treat with an initial dose of methylprednisolone 1 to 2 mg/kg intravenously followed by oral prednisone 1 to 2 mg/kg per day. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- Hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and electrolyte abnormalities (such as hyponatremia and hyperkalemia) constitutes adrenal crisis.
- Hospitalization and endocrine consultation should be considered.

Grade 4 events:

- Discontinue pembrolizumab.
- Manage as per Grade 3

Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

Grade 2 events (and Grade 3-4 hypothyroidism):

- Monitor thyroid function or other hormonal level tests and serum chemistries more frequently until returned to baseline values.
- Thyroid hormone and/or steroid replacement therapy to manage adrenal insufficiency.
- Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted.
- In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
- In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
- Consultation with an endocrinologist may be considered.

Grade 3 hyperthyroidism events:

- Hold pembrolizumab.
- Rule out infection and sepsis with appropriate cultures and imaging.
- Treat with an initial dose of methylprednisolone 1 to 2 mg/kg intravenously followed by oral prednisone 1 to 2 mg/kg per day. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:

- Discontinue pembrolizumab.
- Manage as per Grade 3

A2.4 Hematologic

All attempts should be made to rule out other causes such as metastases, sepsis and/or infection. Relevant diagnostic studies such as peripheral blood smear, reticulocyte count, LOH, haptoglobin, bone marrow biopsy or Coomb's test, etc., should be considered to confirm the diagnosis.

Course of Action
Grade 2 events:

- Hold pembrolizumab
- Prednisone 1-2 mg/kg daily may be indicated
- Consider Hematology consultation.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 3 events:

- Hematology consultation.
- Hold pembrolizumab Discontinuation should be considered as per specific protocol guidance.
- Treat with methylprednisolone 125 mg iv or prednisone 1-2 mg/kg p.o. (or equivalent) as
- appropriate
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:

- Hematology consultation
- Discontinue pembrolizumab for all solid tumor indications; refer to protocol for hematologic
- malignancies.
- Treat with methylprednisolone

3.5 Hepatic

Course of Action

Grade 2 events:

- Hold pembrolizumab
- Monitor liver function tests more frequently until returned to baseline values (consider weekly).

- Treat with 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns
- to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic
- antibiotics for opportunistic infections, and resume pembrolizumab per protocol
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- Permanently discontinue pembrolizumab for patients with liver metastasis who begin treatment with Grade 2 elevation of AST or ALT, and AST or ALT increases 50% relative to baseline and lasts 1 week.

Grade 3 events:

- Discontinue pembrolizumab when AST or ALT >5.0 times ULN and/or total bilirubin >3.0 times ULN.
- Consider appropriate consultation and liver biopsy to establish etiology of hepatic injury, if necessary
- Treat with high-dose intravenous glucocorticosteroids for 24 to 48 hours.
    - When symptoms improve to Grade 1 or less, a steroid taper with dexamethasone 4 mg every 4 hours or prednisone at 1 to 2 mg/kg should be started and continued over no less than 4 weeks.
- If serum transaminase levels do not decrease 48 hours after initiation of systemic steroids, oral mycophenolate mofetil 500 mg every 12 hours may be given. Infliximab is not recommended due to its potential for hepatotoxicity.
- Several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:

- Permanently discontinue pembrolizumab
- Manage patient as per Grade 3 above

A2.6 Neurologic

All attempts should be made to rule out other causes such as metastatic disease, other medications or infectious causes.

Course of Action

Grade 2 events:

- Moderate (Grade 2) - consider withholding pembrolizumab.

- Consider treatment with prednisone 1-2 mg/kg p.a. daily as appropriate
- Consider Neurology consultation. Consider biopsy for confirmation of diagnosis.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 3 and 4 events:

- Discontinue pembrolizumab
- Obtain neurology consultation. Consider biopsy for confirmation of diagnosis
- Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day. If condition worsens consider IVIG or other immunosuppressive therapies as per local guidelines
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

A2.7 Ocular

All attempts should be made to rule out other causes such as metastatic disease, infection or other ocular disease (e.g. glaucoma or cataracts). However the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:

- Evaluation by an ophthalmologist is strongly recommended.
- Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitics.
- Discontinue pembrolizumab as per protocol if symptoms persist despite treatment with topical immunosuppressive therapy.

Grade 3 events:

- Evaluation by an ophthalmologist is strongly recommended
- Hold pembrolizumab and consider permanent discontinuation as per specific protocol guidance.
- Treat with systemic corticosteroids such as prednisone at a dose of 1 to 2 mg/kg per day.
    - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:

- Evaluation by an ophthalmologist is strongly recommended
- Permanently discontinue pembrolizumab.
- Treat with corticosteroids as per Grade 3 above

A2.8 Renal

All attempts should be made to rule out other causes such as obstructive uropathy, progression of disease, or injury due to other chemotherapy agents. A renal consultation is recommended. However the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:

- Hold pembrolizumab
- Treatment with prednisone 1-2 mg/kg p.o. daily.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 3-4 events:

- Discontinue pembrolizumab
- Renal consultation with consideration of ultrasound and/or biopsy as appropriate
- Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone IV or equivalent once per day.
    - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

A2.9 Skin - Rash and Pruritus

Course of Action

Grade 2 events:

- Symptomatic treatment should be given such as topical glucocorticosteroids (e.g., betamethasone 0.1% cream or hydrocortisone 1%) or urea-containing creams in combination with oral antipruritics (e.g., diphenhydramine HCl or hydroxyzine HCl).
- Treatment with oral steroids is at physician's discretion for Grade 2 events.

Grade 3 events:

- Hold pembrolizumab.
- Consider Dermatology Consultation and biopsy for confirmation of diagnosis.

- Treatment with oral steroids is recommended, starting with 1 mg/kg prednisone or equivalent once per day or dexamethasone 4 mg four times orally daily.
    - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:

- Permanently discontinue pembrolizumab.
- Dermatology consultation and consideration of biopsy and clinical dermatology photograph.
- Initiate steroids at 1 to 2 mg/kg prednisone or equivalent.
    - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

A2.10 Other

All attempts should be made to rule out other causes. Therapeutic specialists should be consulted as appropriate.

Course of Action

Grade 2 events or Grade 1 events that do not improve with symptomatic treatment:

- Withhold pembrolizumab.
- Systemic corticosteroids may be indicated.
- Consider biopsy for confirmation of diagnosis.
- If pembrolizumab held and corticosteroid required, manage as per grade 3 below.

Grade 3 events:

- Hold pembrolizumab
- Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks. Otherwise, pembrolizumab treatment may be restarted and the dose modified as specified in the protocol

Grade 4 events:

- Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day.
- Discontinue pembrolizumab