A PHASE I/II TRIAL OF EPACADOSTAT (INDOLAMINE 2,3 DIOXYGENASE INHIBITOR), INTRALESIONAL SD-101 (TOLL-RECEPTOR 9 AGONIST), AND RADIOTHERAPY IN PATIENTS WITH ADVANCED SOLID TUMORS AND LYMPHOMA

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PROTOCOL SIGNATURE PAGE

Protocol Number: UCDCC#271

Protocol Title: A Phase I/II Trial of Epacadostat (Indolamine 2,3 Dioxygenase Inhibitor), Intralesional SD-101 (Toll-Receptor 9 Agonist), and Radiotherapy in Patients with Advanced Solid Tumors and Lymphoma

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated, in accordance with all stipulations of the protocol and in accordance with Good Clinical Practices, local regulatory requirements, and the Declaration of Helsinki.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study agent(s) and the conduct of the study.

_____
Investigator Name (print)

_____
Investigator Signature

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Date

LIST OF ABBREVIATIONS

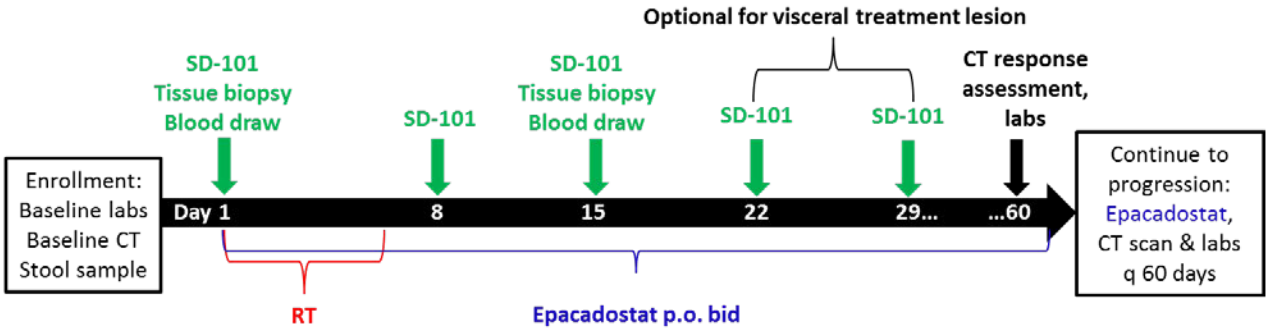
ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AESI	Adverse event of special interest
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase/serum glutamic pyruvic transaminase/SGPT
aPTT	Activated partial thromboplastin time
ARR	Abscopal Response Rate
AST	Aspartate aminotransferase/serum glutamic oxaloacetic transaminase/SGOT
BCRP	Breast Cancer Resistant Protein
BID	Twice a day
CNS	Central nervous system
CR	Complete response
CRF	Case Report/Record Form
CRP	C-reactive protein
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTV	Clinical target volume
DCR	Disease control rate
DFS	Disease free survival
DLco	diffusing capacity of the lung for carbon monoxide
DLT	Dose limiting toxicity
DVH	Dose volume histogram
ECOG	Eastern Cooperative Oncology Group
ERS	Epacadostat + radiotherapy + SD-101
FACS	Fluorescence-activated cell sorting
FDA	U.S. Food and Drug Administration
FFPE	Formalin fixed paraffin embedded
FNA	Fine needle aspiration
GTV	Gross tumor volume
Hr	Hour
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
hPXR	Human pregnane X receptor
i.v.	Intravenous(ly)
ICH	International Conference on Harmonization
IDO1	Indoleamine 2,3-dioxygenase 1
IEC	Independent Ethics Committee
IHC	Immunohistochemical
IDO	Indolamine 2,3 Dioxygenase
IMP	Investigational medicinal product

IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
irAE	immune-related adverse event
irRECIST	Immune Related RECIST
ITV	Internal target volume
IV	intravenous
LVEF	left ventricular ejection fraction
LFTs	Liver function tests
MAOI	Monoamine Oxidase Inhibitor
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NSCLC	Non small cell lung cancer
ODN	Oligodeoxynucleotide
ORR	Objective response rate
OS	Overall survival
PBMC	peripheral blood mononuclear cell
PD	Progressive disease
PD-1	Programmed death-1
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PK	Pharmacokinetic
PR	Partial response
PTV	Planning treatment volume
REB	Research Ethics Board
RECIST	Response Evaluation Criteria in Solid Tumors
RT	Radiotherapy
SAE	Serious Adverse Event
SD	Stable disease
SS	Serotonin syndrome
SSRI	Selective serotonin reuptake inhibitors
SUSAR	Suspected Unexpected Serious Adverse Reaction
TDLN	Tumor draining lymph nodes
TLR9	Toll-like receptor 9
TNF	Tumor necrosis factor
TSH	Thyroid-stimulating hormone
SOP	Standard Operating Procedure
UCDCC	UC Davis Comprehensive Cancer Center
ULN	Upper limit of normal

SCHEMA

General Enrollment Criteria

- Advanced refractory solid tumors or lymphoma
- Age ≥18
- 14 day treatment washout period
- At least one candidate treatment lesion (subcutaneous, nodal, or visceral)
  - Accessible for RT
  - Accessible and safe for repeat intralesional injections
- At least one candidate target lesion, outside of the RT field evaluable for response per irRECIST
- Adequate hematologic and end organ function
- No active autoimmune disease
- Patients with previous checkpoint blockade therapy are eligible



Concurrent RT (Days 1-5)

- Cohort 1 (solid tumors): (8 Gy x 3) or (4 Gy x 5)
- Cohort 2 (lymphoma): (8 Gy x 3) or (4 Gy x 5) or (2 Gy x 2)

+

Intralesional SD-101 (Day 1, 8, 15, 22, 29)
4 mg injection into RT treatment lesion

+

Epacadostat
50-300 mg PO bid

Phase I Dose Finding

3+3 Design: (3-6 patients per dose level, 6-18 patients total)

Dose level -3:	50 mg PO bid
Dose level -2:	100 mg PO bid
Dose level -1:	200 mg PO bid
Dose level 1:	300 mg PO bid

Phase II Expansion Cohorts

Simon Two-Stage Design

Cohort 1:	Solid tumor (16-30 patients) P0=0.05, p1=0.20, r1=1, n1=16, rTot=3, nTot=30, α=0.05, power=0.8
Cohort 2:	Lymphoma (7-14 patients) P0=0.05, p1=0.3, r1=0, n1=7, rTot=2, nTot=14, α=0.05, power=0.8

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1. OBJECTIVES

1.1 Primary Objective

1.1.1 Phase 1: To determine the maximum tolerated dose (MTD) of epacadostat that can be given with radiotherapy and intralesional SD-101 immunotherapy (ERS: Epacadostat + radiotherapy + intralesional SD-101).

1.1.2 Phase 2: To characterize the safety profile of this regimen using CTCAE v4.03 (Common Toxicity Criteria for Adverse Events version 4.03).

1.2 Secondary Objectives

1.2.1 To provide efficacy data for ERS as determine by abscopal response rate (defined as objective response rate at unirradiated sites) using immune related RECIST (irRECIST) and disease control rate (DCR) defined as complete response (CR) + partial response (PR) + stable disease (SD).

1.2.2 To determine treatment tolerability.

1.3 Exploratory Objectives

1.3.1 To provide preliminary data on the objective response rate (ORR), progression free survival (PFS), and overall survival (OS) for ERS therapy using irRECIST and RECIST1.1 criteria.

1.3.2 To analyze serial blood samples for serum cytokine and tryptophan / kynurenine levels, and to quantify the number, function, and gene expression of circulating immune cell subsets.

1.3.3 To evaluate serial tumor tissue biopsies for tumor infiltrating immune cell subsets, expression of immune regulatory proteins including IDO and PD-L1, gene expression signatures, and mutational load.

1.3.4 To evaluate pre-treatment stool samples for microbiome signatures

1.3.5 To discover biomarkers of response from the data obtained in 1.2, 1.3.1, 1.3.2, 1.3.3, and 1.3.4.

2. BACKGROUND

2.1 Cancer Immunotherapy

The allure of cancer immunotherapy as a magic bullet against cancer has intrigued researchers for over a century. The rationale underlying anti-cancer immunotherapy stems from the concept of immune surveillance first attributed to Ehrlich and colleagues over a century ago [1]. It was founded in the idea that tissue rejection is actually a manifestation of an immune surveillance mechanism that guards against spontaneous arising tumors. If such a mechanism does exist then it stands to reason that it can be re-invigorated and harnessed to battle malignancy in cancer patients. This idea, in its simplest form, is particularly attractive given that the immune system should be able to identify and specifically eradicate malignant cells based on the expression of abnormal antigens not expressed or present in normal tissues [2]. On a cellular level antigen presenting cells (APCs), such as dendritic cells, phagocytize fragments of dying cancer cells and present them on their cell surface. CD8+ T cells can recognize these abnormal antigens and become activated to kill cells expressing that antigen. CD4+ T cells can either help this process by expressing ligands and cytokines which help activate and sustain the APCs or they can become immunosuppressive regulatory T cells (Tregs) which express FOXP3 (forkhead box P3) and inhibit CD8+ T cells. In reality this is a gross oversimplification and the true complexity of the interactions between the host immune system and cancer are not fully understood but many cell types and factors are involved.

2.2 Rationale: RT + Intralesional CpG + IDO blockade

There is growing interest in understanding mechanisms of resistance to immunotherapy and finding combinatorial strategies to further increase efficacy while minimizing toxicity.

Local radiotherapy (RT) is an ideal candidate for combined modality immunotherapy strategies. In addition to debulking tumor and releasing tumor antigens, RT has well-established immunomodulatory effects [3]. Preclinical and clinical reports confirm the safety and efficacy of multimodality strategies employing RT and immunotherapy. One particularly promising strategy is RT in combination with the immune stimulatory toll-like receptor 9 (TLR9) agonist CpG oligodeoxynucleotide (CpG), which has demonstrated significant synergy in pre-clinical models [4] and the ability to induce regression of systemic disease in clinical trials [5, 6]. Systemic response rates were about 20% with disease stability in another 20% of patients with refractory systemic [5] or cutaneous lymphoma [6]. However, patients whose tumors induced Tregs responded poorly. The effects of CpG on Treg mediated immune suppression can be paradoxical. CpG can reduce Tregs by converting them to a T-helper phenotype via IL-6 production [7] and can also directly reverse Treg function [8]. Conversely, CpG can directly induce Foxp3 expression [9] and up-regulate indolamine-2,3-dioxygenase (IDO) [7] which is known to induce and maintain Tregs.

IDO is an immunosuppressive enzyme that catalyzes the rate-limiting step in the catabolism of tryptophan to kynurenine and is expressed by numerous human malignancies [10, 11]. IDO expression can induce immune tolerance to malignancies [12] via complex mechanisms [13]. In dendritic cells IDO can activate Treg suppressive function in a CTLA-4 dependent manner [14]. It can also prevent dendritic cell IL-6 production, thereby preventing Treg conversion and maintaining elevated Treg levels despite inflammatory signals such as CpG [15]. Furthermore, IDO can directly induce Tregs from naïve CD4+ T cells via 3-hydroxyanthranillic acid, a downstream catabolite of IDO tryptophan metabolism [16, 17]. IDO can, through similarly complex mechanisms, inhibit natural killer cells and prevent effector T-cell activation and proliferation [13, 18]. IDO expression can be paradoxically upregulated after inflammatory signals [19, 20] presumably as a mechanism to limit inflammation and maintain immune homeostasis.

In murine studies and a canine clinical trial we have demonstrated that IDO upregulation by RT + CpG limits the response to this therapy and that addition of IDO blockade improves therapeutic efficacy. We hypothesize that the addition of IDO blockade will improve upon the known historical efficacy of RT + CpG therapy, and will be highly effective and well tolerated in the management of advanced solid tumors and lymphomas.

2.3 Pre-clinical data

Using a novel immunotherapy strategy combining local RT, intratumoral CpG, and IDO blockade, we tested the hypothesis that IDO upregulation after RT + CpG maintains tumor microenvironment immune suppression and limits treatment efficacy. We found that immunostimulatory therapies, including CpG and RT, can paradoxically up-regulate IDO expression (Figure 1a-c). The addition of IDO blockade (using 1-methyl tryptophan) to RT + CpG therapy decreased IDO activity, and significantly improved the anti-tumor effects of RT + CpG both in terms of local tumor growth and systemic metastases (Figure 1d-l). Mechanistically, the triple therapy decreased Tregs (Figure 2a-c), other immune suppressive factors (data not shown), increased tumor-infiltrating CD8+ T-cells within the tumor micro-environment and the anti-tumor effects were CD8+ T-cell dependent (Figure 3). Although the immune effects were primarily limited to the microenvironment of the treated tumor, robust systemic anti-tumor responses were observed. We confirmed these results in a veterinary clinical trial of companion canines since canine cancers closely represent human malignancy (Figure 4). We observed significant responses at the RT treated primary tumor (Figure 4a-d) as well as at untreated sites of metastatic disease (Figure 4e-h) in most dogs with an 80% systemic disease control rate even though the treatment regimen only lasted 28 days. We also observed significant changes in the immunosuppressive tumor micro-environment in canines (Figure 2d-g), corroborating our mechanistic mouse data. In marked contrast to immune checkpoint inhibitors, little toxicity was observed in mouse or canine studies. These results confirm the potency of this combinatorial immunotherapy strategy and suggest that the

addition of IDO blockade may safely improve the efficacy of RT + CpG immunotherapy. The safety and efficacy make this strategy very attractive for clinical translation.

Figure 1. 1MT Limits Radiation + CpG Induced IDO Up-Regulation and Improves Therapeutic Efficacy

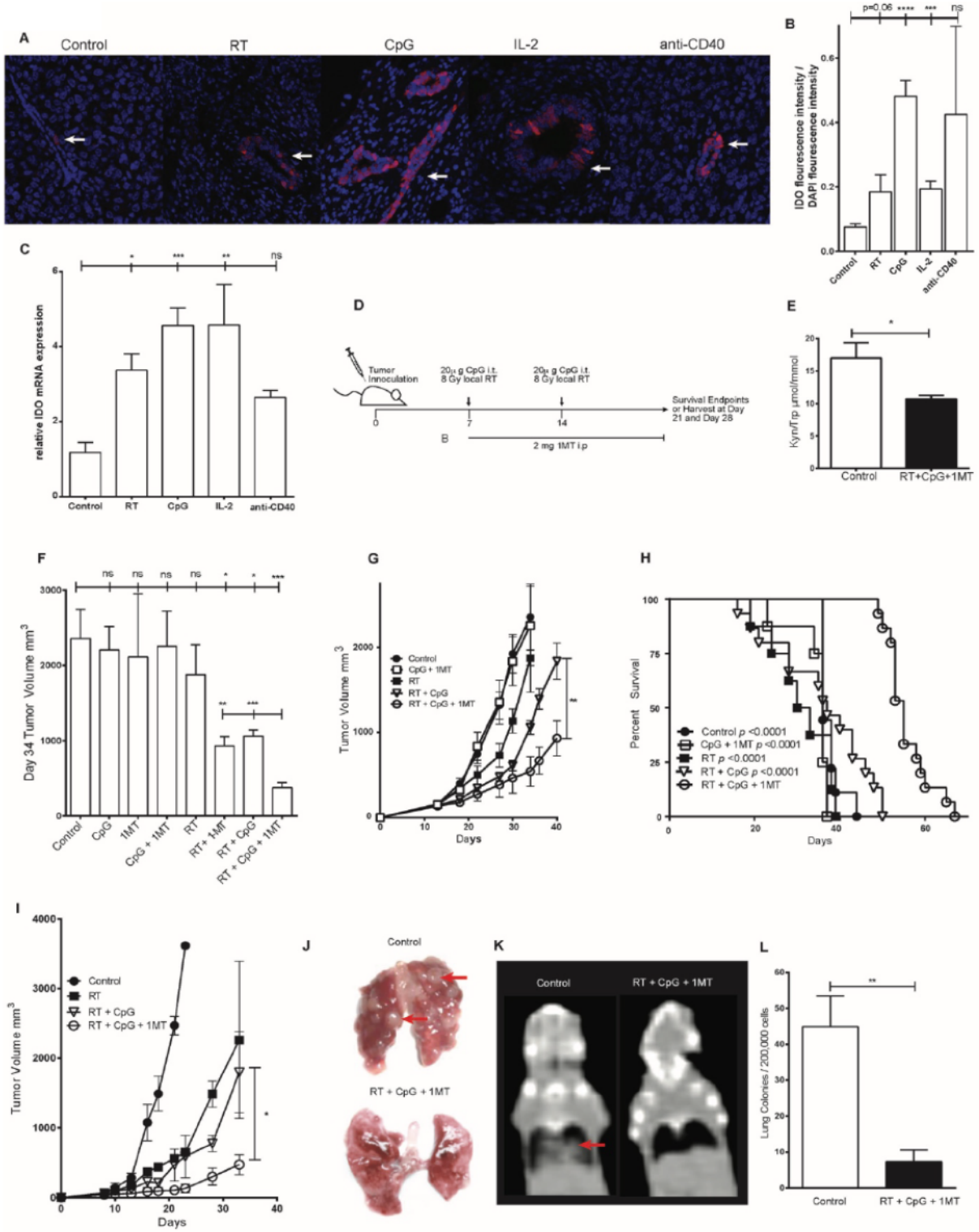


Figure 2. Radiation + CpG + 1MT Reduces Intratumoral Regulatory CD4+ T-cells in Mice and Canines.

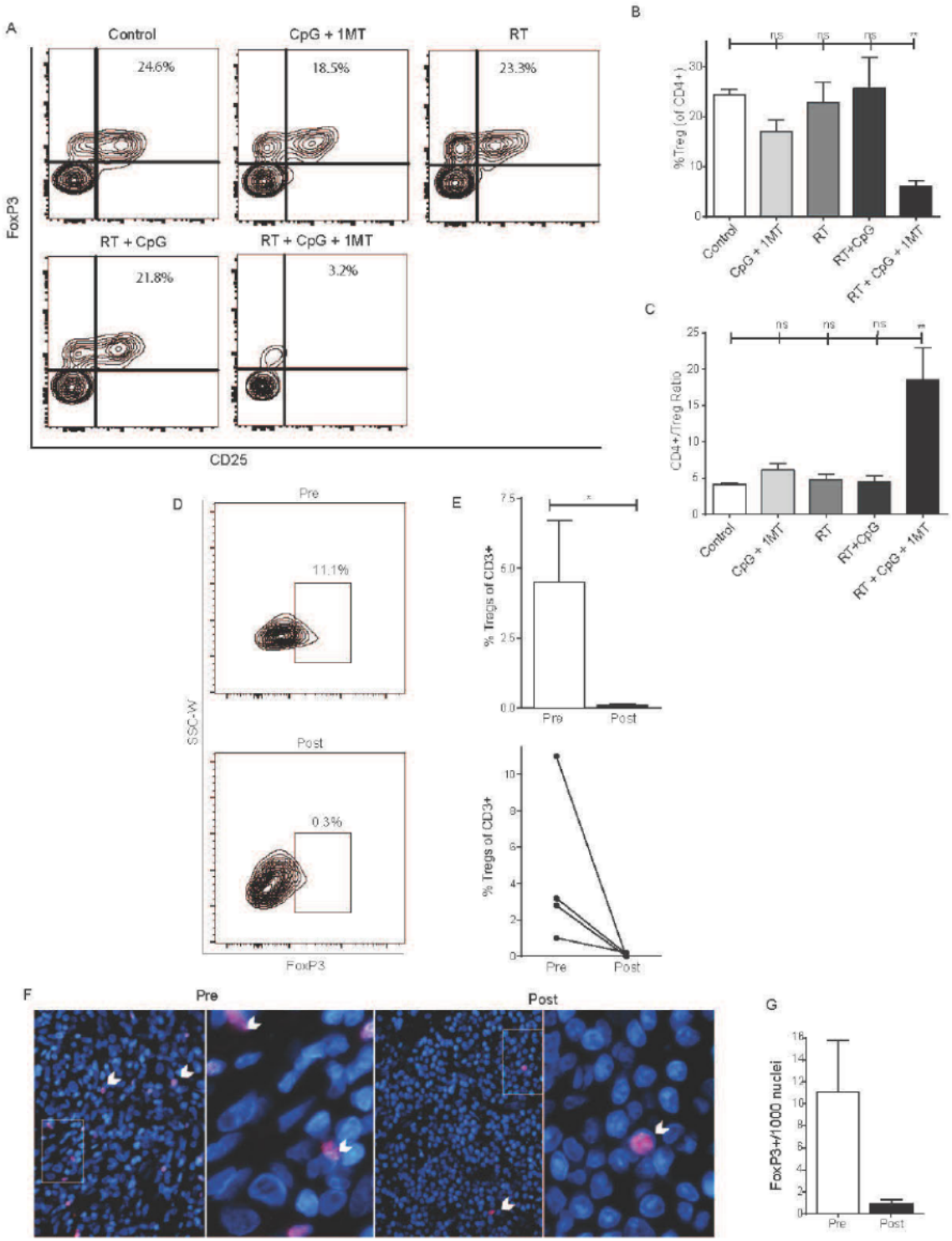
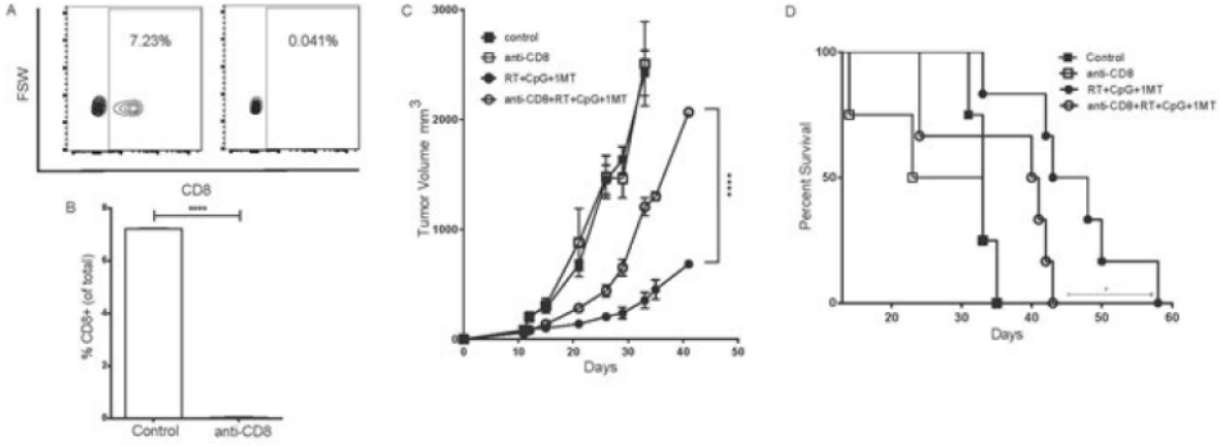


Figure 1. Expression of IDO in control or treated 4T1 tumors by immunofluorescence (A, B) or qPCR (C). IDO + cells stain bright pink and nuclei are counterstained by DAPI, white arrows indicate examples of positive staining cells. Balb/c mice bearing orthotopic 4T1 breast tumors or C57/BL6 mice bearing B16 melanoma tumors were treated as outlined in the schema (D). IDO enzymatic activity in 4T1 tumor bearing mice as measured by serum kynurenine to tryptophan ratio (E). 4T1 tumor growth (F,G) and tumor bearing mouse survival (H). B16 melanoma tumor growth (I). Lung metastases in orthotopic 4T1 bearing mice as assessed by gross examination (J), computed tomography (K), and lung colony forming assay (L). Red arrows indicate examples of lung metastases. n=3-4 mice per group for correlative studies and n=6-10 mice per group for tumor growth studies and survival studies. Bar graphs represent mean +/- standard error of mean. Results analyzed by one-way ANOVA, student's t-test, or kaplan-meier analysis between the indicated groups (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$).

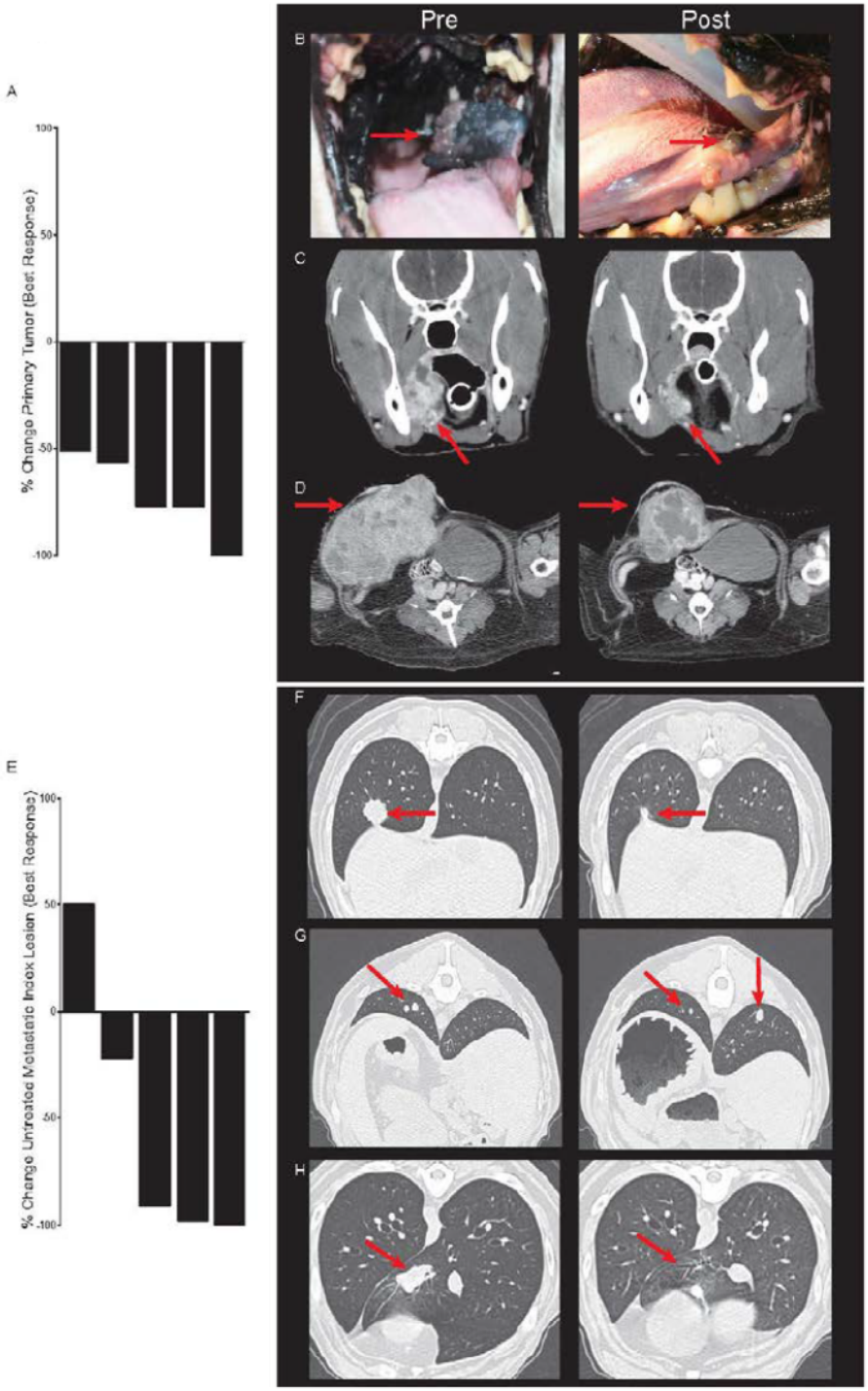
Figure 2. Day 28 levels of tumor infiltrating regulatory CD4+ T-cells as assessed by flow cytometry and immunofluorescence in 4T1 bearing mice (**A**-**C**) or canine patients (**D**-**G**) treated with RT + CpG + 1MT. Representative flow cytometry contour plots demonstrating staining of intratumoral CD4+ cells for FoxP3 and CD25 (**A**). Flow cytometry data represented as a bar graph expressed as %Treg (CD4+,CD25+,FoxP3+) of CD4+ cells (**B**). Bar graph representation of CD4+ to Treg ratio as measured by flow cytometry (**C**). Representative flow cytometry plots demonstrating staining of canine intratumoral CD4+ cells for FoxP3 pre- and post- RT + CpG + 1MT therapy (**D**). Bar graph representation of intratumoral Tregs pre- and post-therapy expressed as a percentage of CD3+ cells in four canine patients as assessed by flow cytometry (**E**). Line graph demonstrates changes in Treg levels in individual patients as assessed by flow cytometry (**E**). Immuno-fluorescent staining of canine tumor samples for FoxP3 (**F**). FoxP3 + cells stain bright pink and nuclei are counterstained by DAPI, white arrows point out examples of positive staining cells. Bar graph quantification of intratumoral FoxP3 positive cells (**G**). n=3-4 mice per group and four canines patients. Bar graphs represent mean +/- standard error of mean. Results analyzed by one-way ANOVA or student's t-test between the indicated groups (* $p < 0.05$, ** $p < 0.01$).

Figure 3. Anti-tumor Effects of Radiation + CpG + 1MT are CD8+ T cell Dependent



Balb/c mice bearing orthotopic 4T1 breast tumors were depleted of CD8+ T cells with 500ug i.p. injections of anti-CD8 antibody administered once weekly (A-D). Levels of circulating CD8+ T cells as assessed by flow cytometry in 4T1 bearing mice (A-B). Representative flow cytometry contour plots demonstrating staining of CD45+CD3+ cells for CD8 (A). Flow cytometry data represented as a bar graph expressed as % CD8+ cells of all peripheral blood mononuclear cells (B). Tumor growth (C) and survival (D) of 4T1 bearing mice treated with triple therapy and / or CD8 depletion. n=6-10 mice per group. Bar graphs represent mean +/- standard error of mean. Results analyzed by ANOVA, student's t-test, or kaplan-meier analysis between the indicated groups (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$).

Figure 4. Efficacy of Radiation + CpG + 1MT in a Canine Clinical Trial



Therapeutic response of local irradiated tumors (**A**-**D**) and untreated metastatic lesions (**E**-**H**) in a canine clinical trial are depicted. Waterfall plot of best response at the primary treated tumor (**A**). Photographs (**B**) and computed tomography (**C**) depicting response of a melanoma of the buccal mucosa. Computed tomography depicting response of an abdominal wall sarcoma (**D**). Waterfall plot of best response at untreated metastatic index lesions (**E**). Computed tomography demonstrating a partial response (**F**), mixed response (**G**), and complete response (**H**) of metastatic pulmonary index lesions.

2.4 Epacadostat

Epacadostat (INCB024360) is an inhibitor of the enzyme indoleamine 2,3-dioxygenase 1 (IDO1) that is proposed for development for the treatment of malignant diseases. 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 [21], 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 [22]. 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.

2.4.1 Pharmacology Summary

Epacadostat represents a novel, potent, and selective inhibitor of the enzyme IDO1. Because IDO1 catabolism of Trp inhibits T-cell – –mediated immune responses and IDO1 expression has been shown to be elevated in many human cancers, 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.

To assess its selectivity profile, epacadostat was evaluated in a broad panel of approximately 55 different receptors, ion channels, transporters, and non-kinase enzymes. Epacadostat demonstrated activity at the human vasopressin 1a receptor (IC50 value = 0.67 μM). And weak activity at the human dopamine transporter (22% and 71% inhibition at 1 and 10 μM, respectively) and human carbonic anhydrase II enzyme (IC50 = 5.3 μM). In cell culture, epacadostat reverses the strong inhibitory effect on the development of T-cell-mediated responses that IDO1 activity imparts, resulting in enhanced T-cell and natural killer (NK) cell proliferation, enhanced interferon gamma production, reduced regulatory T lymphocyte (Treg) differentiation, reduced DC apoptosis, and enhanced expression of DC activation markers. Epacadostat reversal of the IDO1-mediated suppression of T-cell proliferation is dose dependent with a potency consistent with its inhibition of Trp to Kyn conversion (EC50 = 17.7 nM). The *in vivo* data demonstrate that epacadostat can inhibit IDO1

systemically and, importantly, in tumors and tumor draining lymph nodes (TDLN). Epacadostat was efficacious in mouse models of colon and pancreatic cancer, and its ability to reduce tumor growth was dependent on a functional immune system, consistent with its proposed mechanism of action. Moreover, epacadostat enhanced lymphocyte function in tumors and TDLN. The combination of epacadostat and either an anti-mouse CTLA4 or an anti-mouse PDL1 antibody was also shown to act synergistically in significantly reducing tumor growth in a melanoma xenograft model. Finally, epacadostat improved the tumor growth control of cytotoxic chemotherapy when used in combination. These data support the evaluation of epacadostat in patients with malignant diseases. Epacadostat did not produce any adverse effects after a single oral dose to rats (1000 mg/kg) in central nervous system (CNS) or respiratory safety pharmacology studies, and no adverse effects were noted in a cardiovascular study in telemeterized dogs. The IC50 for the inhibitory effect of epacadostat on human ether-à-go-go-related gene (hERG) potassium current was 219.5 µM. This value is approximately 1500-fold over the unbound human Cmax value at a maximum clinical dose of 600 mg.

2.4.2 Nonclinical Drug Metabolism and Pharmacokinetics Summary

In vitro and *in vivo* studies were conducted to characterize the absorption, distribution, metabolism, and excretion (ADME) profile of epacadostat. In pharmacokinetic (PK) studies conducted in mice, rats, cynomolgus monkeys, and beagle dogs, epacadostat exhibited oral bioavailability values ranging from 11% to 55%. The total systemic clearance (CL) was moderate in mice (2.5 L/h/kg), rats (males 1.1, females 1.9 L/h/kg), cynomolgus monkeys (0.81 L/h/kg), and dogs (0.46 L/h/kg) after intravenous (IV) administration, with hepatic extraction ratios of approximately 24% to 58%. Epacadostat exhibited a moderate volume of distribution (Vdss) and the terminal half-life values after IV doses ranged from 1.4 to 3.3 hours in the various species studied. Protein binding of epacadostat was high, with mean *ex vivo* free fractions of 2.5% in mice and 3.8% in dogs, while the mean *in vitro* free fraction in human plasma was 3.1%.

In the 13-week toxicokinetic studies in mice and dogs, the Cmax and AUC values generally increased with dose, although not always dose proportionally. The AUC values on Day 90 were similar to corresponding values on Day 1, except for the mid- and high-dose groups in mice, where exposures on Day 90 were lower than that on Day 1. No gender differences were observed in dogs; however, the plasma exposure in female mice was greater than that observed in male mice at corresponding dose levels.

Metabolism studies have shown that the enzymes responsible for the formation of the major metabolites, M9 and M11, were UGT1A9 and gut flora, respectively. M12 is a secondary metabolite of epacadostat formed via oxidation of M11 by cytochrome P450 (CYP)3A4 and to a lesser extent by CYP2C19 and CYP1A2. The major plasma analyte present in mice and

human plasma was M9, while epacadostat was the major plasma component in dogs. In vitro transporter studies suggested that epacadostat was likely a substrate of P-gp and Breast Cancer Resistant Protein (BCRP).

The metabolism of epacadostat was examined in the plasma and excreta of mice and bile duct cannulated dogs given a single oral or IV dose of 14C-INCB24360. M9, an O-glucuronide of INCB24360, was the only major metabolite (greater than 10% of total drug-related AUC) radiochemically detected in the plasma of mice, comprising 66.3% to 74.1% of the total AUC. Urinary M9 accounted for 20.8% to 30.8% of the administered dose and was the only metabolite found at levels > 10% of the administered dose in the feces of mice dosed orally with epacadostat. In dog plasma, epacadostat was the only radiochemically detected component from the oral dose group. Biliary M9 accounted for 33.5% (PO) to 47.2% (IV) of administed dose and was considered the only major metabolite formed in dogs. None of the metabolites accounted for >5% of the dog dose in urine. M11 was the only metabolite radiochemically detected in dog feces as levels 1.1% of dose in oral dose group.

Results from the human pregnane X receptor (hPXR) reporter gene assay suggest that the potential for epacadostat to cause induction of CYP3A4 in humans at clinically relevant exposures is low. Epacadostat and its major metabolites, M9, M11, and M12, have low potential to cause drug-drug interactions through CYP and UGT inhibition based on IC50 values. However, based on the *in vitro* IC50 for sorafenib inhibition of UGT1A9 (2.3 μM), there is a potential for drug interactions if administered concomitantly with epacadostat, and further clinical studies may be warranted. Similarly, the potential for epacadostat to cause clinical drug-drug interactions via human uptake transporters OAT1, OAT3, OCT2, and OATP1B1 is low. Based on *in vitro* data, inhibition of hepatic uptake transporter OATP1B3 by M9 and M11 cannot entirely be excluded.

In mice, excretion was rapid and complete after a single oral dose of [^{14}C]epacadostat. After oral administration of [14C]epacadostat at 500 mg/kg in mice, recovery in feces was greater than urinary excretion . After oral dose administration, 33.2% was excreted in the urine and 50.6% was excreted in the feces in females. Blood-to-plasma radioactivity concentration ratios were approximately 0.6 to 0.7 after oral administration in males and females, respectively. This indicates preferential distribution of radioactivity in the plasma portion of blood. A comparison of tissue distribution between nonpigmented and pigmented male mice showed similar patterns of distribution and tissue concentrations, except for higher concentrations of radioactivity in the eye uvea in pigmented mice.

2.4.3 Nonclinical Toxicology Summary

The toxicologic and toxicokinetic profiles of epacadostat were characterized by single and repeat oral dose studies of up to 3 months in duration in mice and dogs. Assessments of potential genetic toxicity were conducted using *in vitro* and *in vivo* test systems.

Oral administration studies in mice, rats, and dogs were conducted in order to assess the potential systemic toxicity of epacadostat. In single dose studies, doses up to 4000 mg/kg in mice, up to 1000 mg/kg in rats, and up to 540 mg/kg in dogs did not compromise the salubrity of the animals. In repeat oral dose studies in mice, no adverse epacadostat-related effects were observed in any parameter evaluated. The no-observed-adverse-effect-level (NOAEL) for male and female mice given epacadostat for 3 months was 1000 mg/kg per day. In the 3-month repeat oral dose study in dogs, 1 male given the high dose of 1000 mg/kg per day was sacrificed moribund on Day 29 of the administration phase because of poor condition associated with liver inflammation. Slightly increased liver enzymes noted in this animal during the predose phase suggested that epacadostat may have exacerbated a pre-existing liver condition. Clinical observations associated with epacadostat administration in the 3-month dog study included thin appearance and increased incidence of emesis and diarrhea (> 250 mg/kg per day) and lower food consumption and body weight loss (1000 mg/kg per day). Microscopic findings included lymphangectasia in the small intestine (> 250 mg/kg per day), hepatocellular hypertrophy, lymphoid depletion of the thymus, and chronic inflammation with fibrosis and subacute inflammation in the large intestine (1000 mg/kg per day). With the exception of lymphangiectasia in the jejunum, all epacadostat-related findings had reversed after the 4-week recovery period. The highest non–severely toxic dose (HNSTD) and NOAEL were 250 mg/kg per day based on the reversibility of the lesions observed at this dose level.

Epacadostat was found to be devoid of clastogenic or mutagenic potential in *in vitro* bacterial reverse mutagenicity and chromosome aberration assays as well as in an *in vivo* bone marrow micronucleus test in rats.

2.4.3.1 Potential Risks

In the 3-month dog study, liver inflammation necessitated the euthanasia of a single male given the high dose of 1000 mg/kg per day. Serum chemistry evaluations revealed elevated liver enzymes (aspartate transaminase [AST], alanine transaminase [ALT], gamma-glutamyl transferase [GGT], and alkaline phosphatase [ALP]) along with elevated total bilirubin. Liver inflammation was confirmed histologically. Although this animal had slight liver enzyme elevations during the prestudy period, suggesting a pre-existing liver condition, an effect of epacadostat on the liver cannot be ruled out. Additional findings in repeat oral dose dog studies included an increased incidence of emesis and diarrhea. Human subjects will have liver function tests (LFTs) closely monitored during participation in clinical studies and will be monitored for any signs of GI distress including diarrhea, nausea, vomiting, and/or abdominal pain. Therapy will be withdrawn or interrupted until resolution if there are signs of significant gastrointestinal distress and/or clinically relevant elevations in LFTs.

The mean AUC0-24 associated with the NOAEL of 250 mg/kg per day from the dog 3-month study is 639 µM-h total (24.3 uM-h unbound) abd us approximately 17-fold higher than the

clinical AUC0-24 associated with the highest proposed dose to be further studied clinically (600 mg twice a day [BID]).

Theoretically, IDO1 represents an important immune control enzyme. Cells expressing IDO1 are capable of suppressing amplified immune effect or responses and promoting immune tolerance under various physiological conditions. Inhibition of the IDO pathway using 1-methyl tryptophan (1-MT) has been shown to induce fetal allograft rejection in mice [23]. Syngeneic pluripotent bone marrow stem cells, transferred to mice with experimental autoimmune encephalomyelitis (a model of multiple sclerosis), enhanced recovery, prevented relapses, and promoted myelin repair through their expression of IDO. This was blocked by administration of 1-MT [24], and inhibition of the IDO pathway by systemic administration of 1-MT at clinical onset significantly exacerbated disease scores in this model [25]. Blocking IDO with 1-MT also aggravated the severity of arthritis and enhanced the immune responses in mice with collagen-induced arthritis [26]. Recent studies with the anti-CTLA-4 antibody ipilimumab have shown dysregulation of mucosal immunity and gastrointestinal toxicity, which manifests as diarrhea [27] as well as increase in liver enzymes such as ALT and AST. For these reasons, subjects with a history of autoimmune disease were excluded from participation in all current studies with epacadostat, and study participants were closely monitored for signs or symptoms of developing autoimmune or inflammatory disease.

Inhibition of IDO could cause an increase in serotonin levels that could cause a cluster of adverse events (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 (MAO) inhibitors and combinations of serotonergic drugs [28]. The clinical manifestations of SS range from barely perceptible to lethal; onset is rapid (within 12 hours of drug 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 administration, 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 Trp metabolism in the brain that might impact brain serotonin levels. Although this represents a theoretical risk only, use of MAO inhibitors will be prohibited, and all subjects and sites will be informed of the potential risk. Sites will also be presented with procedures for subjects exhibiting SS or SS-like symptoms.

2.4.4 Clinical Summary

As of 29 OCT 2016, 12 Phase 1 and 2 Incyte-sponsored clinical studies have either been completed or are ongoing. Three clinical studies have completed (Studies INCB 24360-101, INCB 24360-102, and INCB 24360-210). Of the 9 ongoing studies 7 (INCB 24360-201, INCB 24360-202, INCB 24360-203, INCB 4360-204, INCB 24360-110, INCB 24360-301 and

INCB 39110-106) are combination therapy studies. As of 29 OCT 2016, 898 unique subjects have been exposed to INCB024360 as monotherapy (149 subjects) and/or in combination with checkpoint inhibitors (anti−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 JAK inhibitor: 32 subjects).

2.4.4.1 Completed Studies

Study INCB 24360-101 was a completed Phase 1, multicenter, open-label, dose-escalation study in subjects with refractory solid tumors that used a 3 + 3 design to determine the safety and tolerability, PK, and pharmacodynamics of escalating oral doses of epacadostat. Subjects were administered doses of epacadostat ranging from 50 mg once daily (QD) to 700 mg BID. Of the 52 subjects treated, 8 subjects (15.4%) had an AE leading to death. Of these 8 subjects, the cause of death was disease progression in 7 subjects and hypoxia in the remaining subject. During the study, 25 subjects (48.1%) had a serious adverse event (SAE). The most frequently reported SAEs were disease progression (4 subjects, 7.7%), abdominal pain, nausea, and hypoxia (3 subjects each, 5.8%). Treatment-emergent AEs (TEAEs) were reported in all subjects.

Fatigue was the most frequently reported TEAE (36 subjects, 69.2%). Two dose-limiting toxicities (DLTs) occurred; 1 DLT of radiation pneumonitis at the 300 mg BID dose level and 1 DLT of fatigue at the 400 mg BID dose level. A maximum tolerated dose (MTD) was not determined.

In Study INCB 24360-101 after fasted oral administration, epacadostat plasma concentrations attained the peak values (Cmax) typically at 2 hours (median Tmax) postdose; the t1⁄2 was 2.9 hours. A high-fat meal did not cause a statistically significant change in epacadostat plasma exposures; therefore, epacadostat may be administered without regard to food. Inhibition of IDO1 was dose-dependent, and at doses at or above 300 mg BID, epacadostat effectively achieved maximal inhibition of IDO1 activity at trough, as assessed using changes in Kyn levels.

INCB 24360-102 was a Phase 1, single-center, open-label, drug-drug interaction study of epacadostat with warfarin. This was a 2-period study consisting of 2 treatments administered in a fixed sequence. During Period 1 (Days 1-7), subjects received a single dose of warfarin 25 mg orally (PO) on Day 1. During Period 2 (Days 8-21), subjects received epacadostat 300 mg BID PO on Days 8 to 20. On Day 14 of Period 2, subjects also received a single dose of warfarin 25 mg. Eighteen subjects were enrolled in the study. No deaths or SAEs occurred. No TEAE was reported in more than 1 subject each in a given period. TEAE occurred only once in a given period, and no TEAE occurred in both periods for a given subject.

Study INCB 24360-210 was a randomized, open-label, Phase 2 study of epacadostat versus tamoxifen in women with histologically confirmed Federation of International Gynecologists and Obstetricians (FIGO) Stage III or IV epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube carcinoma who have had biochemical-recurrence, defined as an increasing cancer antigen 125 level that was greater than the upper limit of normal (ULN) and successively increasing on 2 consecutive measurements at least 2 weeks apart without clinical or radiographic evidence of disease (at least 2 × ULN on 2 occasions at least 1 week apart without evidence of disease is a UK-specific requirement). Forty-two subjects were enrolled (22 in the epacadostat-treated group and 20 in the tamoxifen-treated group). No subject had an AE leading to death. One epacadostat-treated subject (4.5%) had an SAE of abdominal pain, and 1 tamoxifen-treated subject (5%) had an SAE of ascites. Fatigue was the most frequently reported TEAE in the epacadostat group (8 subjects, 36.4%), followed by nausea (6 subjects, 27.3%), rash (5 subjects, 22.7%) and abdominal distention, constipation, and vomiting (4 subjects each, 18.2%). This study was terminated by the sponsor; no new safety concerns with epacadostat were identified. Subjects were followed according to the Protocol.

2.4.4.2 Ongoing Studies

Study INCB 24360-201 is an ongoing Phase 1/Phase 2 study of epacadostat administered in combination with ipilimumab in subjects with unresectable or metastatic melanoma who may have had 1 or more prior systemic regimens for advanced melanoma. The study has 2 phases. The first phase is an open-label, dose-escalation safety run-in phase. The second phase is a randomized, blinded, placebo-controlled study. Cohorts in Phase 1 include epacadostat 300 mg BID, 100 mg BID, 25 mg BID, 50 mg BID continuous, 50 mg BID intermittent (2 weeks on,1 week off), and 75 mg (50 mg AM/25 mg PM) with ipilimumab 3 mg/kg every 3 weeks.

Study INCB 24360-202 is an ongoing Phase 1/2 study of epacadostat administered in combination with pembrolizumab, with Phase 1 being a dose-escalation phase and Phase 2 being an open-label, single arm, cohort expansion phase. Phase 1 is conducted in subjects with advanced or metastatic solid tumors including Stage IIIB, Stage IV, or recurrent non–small cell lung cancer (NSCLC), melanoma, transitional cell carcinoma of the genitourinary tract, renal cell cancer, triple negative breast cancer, adenocarcinoma of the endometrium, or squamous cell carcinoma of the head and neck (SCCHN) who have disease progression on at least 1 line of therapy for advanced or metastatic cancer (except melanoma). Phase 2 is conducted in subjects with NSCLC, melanoma, transitional cell carcinoma of the genitourinary tract, triple negative breast cancer, SCCHN, ovarian cancer, diffuse large B-cell lymphoma (DLBCL), and clear cell renal cell cancer.

The 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%). 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. Only 12 patients (19%) experienced ≥ Grade 3 treatment-related AE. The most frequently reported ≥ Grade 3 treatment-related AE were rash (8%), elevated lipase (5%), elevated amylase (3%). All other ≥ Grade 3 treatment-related AE occurred in only one patient each. 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.
Study INCB 24360-203 is an ongoing Phase 1/2 open-label study of epacadostat administered in combination with MEDI4736 (durvalumab) in subjects with advanced melanoma, NSCLC, pancreatic cancer, or SCCHN. The dose-escalation part of the study (Phase 1) uses a 3 + 3 design to identify the MTD or pharmacodynamically active dose (PAD) of epacadostat in combination with durvalumab. Phase 2 further explores the safety and efficacy of the MTD or PAD of epacadostat in combination with durvalumab determined in Phase 1 in open-label expansion cohorts in the tumor types described.

Study INCB 24360-204 is an ongoing Phase 1/2, open-label study of epacadostat administered in combination with nivolumab conducted in 2 parts. The first part of the study (Phase 1) consists of a dose-escalation of epacadostat with a starting dose of 25 mg BID to assess the safety and tolerability of epacadostat administered with nivolumab 3 mg/kg every 2 weeks in subjects with select advanced solid tumors and lymphomas. The following tumor types are included in this part: melanoma, NSCLC, colorectal cancer (CRC), SCCHN, ovarian cancer and B cell non-Hodgkin lymphoma (NHL) or Hodgkin lymphoma (HL), including DLBCL. A 3 + 3 design is utilized to identify the MTD. The second part (Phase 2) of the study includes 7 expansion cohorts in tumor types tested in Phase 1 (exception: DLBCL is the only lymphoma permitted) and includes an additional cohort for glioblastoma. In Phase 2, subjects are administered the recommended Phase 2 doses of epacadostat BID in combination with nivolumab 240 mg flat dose every 2 weeks.

Study INCB 24360-110 is a Phase 1 dose-escalation study of epacadostat administered in combination with MPDL3280A (atezolizumab) in subjects with previously treated Stage IIIB, Stage IV, or NSCLC. This study will utilize a 3 + 3 design that will identify the MTD or a PAD of epacadostat in combination with atezolizumab in subjects who have failed a platinum-based chemotherapy regimen for Stage IIIB or Stage IV NSCLC. An expansion cohort (up to approximately 20 subjects) will evaluate the MTD or PAD from the escalation portion of the study to further determine the safety, tolerability, efficacy, PK, and PD in this population. A second expansion cohort (approximately 6-12 subjects) with mandatory pretreatment and post-treatment biopsy requirements will be enrolled to evaluate the change in biomarker expression after initial monotherapy epacadostat treatment and then epacadostat + atezolizumab combination treatment.

INCB 39110-106 is an open-label, Phase 1b, platform study in subjects with advanced or metastatic solid tumors. The study is divided into 2 parts (Part 1a and Part 1b). Part 1a evaluates a JAK inhibitor with JAK1 selectivity (INCB039110) in combination with epacadostat (Group A) and INCB039110 in combination with a PI3K-delta inhibitor (INCB050465; Group B) to determine the MTD or PAD and the recommended Part 1b doses for each combination. Once the recommended dose is identified for each treatment group in Part 1a, subjects with advanced solid tumors are enrolled into expansion cohorts based on treatment history with a PD-1 pathway-targeted agent (Part 1b)..

2.5 SD-101

Bacterial deoxyribonucleic acid (DNA) has long been recognized as having potent stimulatory effects on the immune system, including stimulating rejection of transplantable tumors in mice [29]. This activity is mediated preferentially by specific DNA motifs enriched with cytidine-phosho-guanosine (CpG) dinucleotides and can be replicated by short synthetic oligodeoxynucleotides (ODNs) [30, 31]. CpG-ODNs stimulate specific immune cell types by activation of the innate recognition receptor, Toll-like receptor-9 (TLR9) [32], and have no activity in mice with a homozygous deletion of the TLR9 gene [33].

SD-101, an ODN enriched CpG motifs. It is a 30-mer phosphorothioate (PS) ODN containing juxtaposed CpG motifs with flanking regions, in a self-complimentary palindromic sequence that is designated as a Class C-type sequence (CpG-C). The CpG-C type sequences are an agonist for Toll-like receptor 9 (TLR9) and potent inducers of interferon alpha (IFN-α) production from plasmacytoid dendritic cells (pDCs), as well as pDC maturation and B cell proliferation. Potential mechanisms by which TLR9 stimulation by CpG-ODNs may have a significant antitumor effect include enhancement of innate and T-cell immunity, stimulation of cytokines with direct or indirect antitumor activities (including IFN-α), and production of cytotoxic antibodies [34, 35]. SD-101 Drug Product is a clear to slightly opalescent, colorless to pale yellow solution free of visible particles formulated in phosphate buffered saline. SD-101 is a sterile liquid dosage form that is administered as an intratumoral or subcutaneous injection. No structurally similar compound (ie, CpG-ODN) has been approved as a drug substance for any indication.

Based on studies with cultured human peripheral blood mononuclear cells (PBMCs), CpG-ODNs can stimulate interferon-alpha (IFN-α) and interleukin (IL)-12 production as well as functional maturation in plasmacytoid dendritic cells (pDCs) [36] and can induce proliferation and immunoglobulin (Ig) production in human B lymphocytes (B cells) [37]. Signaling by CpG-ODNs through TLR9 requires active uptake of the ODN as TLR9 is present only in specific intracellular compartments [38]. The TLR9 signaling occurs in 2 distinct intracellular structures, early and late endosomes [39, 40], leading to different outcomes.

SD-101 belongs to the CpG-C class of CpG-ODNs and was selected to stimulate very high levels on IFN-α as well as inducing maturation of pDCs to antigen-presenting cells.

TLR9 stimulation by CpG-ODNs may result in a significant antitumor effect by enhancing innate immunity, adaptive T-cell immunity against tumor-specific antigens, and the cytotoxicity of therapeutic antitumor monoclonal antibodies [41-44]. Additionally, CpG-ODNs have significant adjuvant effects in inducing antibody and T-cell responses to immunogens. TLR9 is highly conserved, and CpG-ODNs can be studied in a variety of species. Nonclinical tumor models have demonstrated *de novo*, enhanced, or prolonged antitumor responses when using CpG-ODNs alone or in conjunction with other active agents. The rodent species used for most antitumor investigations expresses TLR9 on a wider spectrum of cell types, including monocytes and myeloid dendritic cells (mDCs) [45]. Thus, the different results of TLR9 stimulation may complicate direct extension of observations in rodents to humans. CpG-ODNs are an important potential new class of agents deserving further exploration in the treatment of cancers and other therapeutic applications in humans [32, 41].

In nonclinical pharmacology studies, SD-101 is a potent stimulator of IFN-α. Toxicity in primates was characterized by inflammatory changes likely resulting from the immunostimulatory effect of SD-101 and minimal complement activation which is consistent with a known class-effect of ODNs. In nonclinical studies, the absorption in plasma (rats and monkeys) and distribution into tissues (rats) of SD-101 following SC injection were consistent with the pattern previously reported for many other structurally similar ODNs [46]. While the absorption, distribution, metabolism, and elimination (ADME) profile of SD-101 has not formally been examined following intratumoral injection (in nonclinical or clinical studies to date), published clinical studies with another immunostimulatory PS ODN (specifically CpG 7909) for the treatment of cancer administered via SC and intratumoral injections demonstrated both local and systemic effects, suggesting similar bioavailability by both routes [47]. Given the similar bioavailability, and the understanding that SC administration results in appreciable deposition at the site of injection [48], it is likely that intratumoral injection uses a similar mechanism for establishing an ADME profile permitting both local and systemic effects. SD-101 pharmacodynamic effects on the immune system should persist for several days.

In humans, phase 1 trials have been completed with SD-101 in: 1) healthy normal volunteers (Trial DV3-HNV-01), and 2) patients with hepatitis C virus (HCV) infection (DV3-HCV-01). PK assessments from the trials in healthy normal volunteers indicate that SD-101 levels in the plasma peaked 2 to 4 hours after subcutaneous (SC) drug administration and declined after 4 hours. These data are consistent with the plasma disposition of PS ODNs that have a short plasma half-life of hours after SC administration. In another clinical trial of SD-101 in 26 healthy male volunteers (Trial DV3-HNV-01), dose-limiting toxicities of severe headache,

injection site induration, and neck pain were observed in 1 subject given 5.0 mg of SD-101, resulting in a halt in dose escalation and accrual. Additional adverse events (AEs) included influenza-like symptoms such as headache, chills, fatigue, and pyrexia, as well as injection site events such as erythema, induration, and pain. Transient lymphopenia was the most common laboratory abnormality observed. There was no evidence of complement activation, coagulation abnormalities, auto-antibody development, or acute AE syndrome. In the trial of SD-101 in 34 patients with chronic HCV infection, up to 5.0 mg of SD-101 was administered alone or in combination with ribavirin (Trial DV3-HCV-01). The majority of AEs were injection site reactions (injection site erythema, injection site swelling, injection site pain, and injection site pruritus), influenza-like symptoms, pyrexia, and myalgia. Most AEs were mild or moderate in reported severity. One patient in the SD-101 0.1 mg/ribavirin group experienced an SAE of hyperthyroidism that was considered probably related to SD-101 and unrelated to ribavirin. No deaths occurred during the trial. A trial of intratumoral SD-101 in combination with low-dose local radiation (XRT) is ongoing in patients (IND 122809) with untreated low-grade non-Hodgkin's lymphomas who do not require immediate systemic therapy (DV3-LYM-01). In DV3-LYM-01, 3 patients have received 5 intratumoral doses of SD-101 1.0 mg, and 3 patients have received 5 intratumoral doses of SD-101 2.0 mg. No DLT was observed and the most common AEs were transient flu-like illness in the 2.0 mg cohort. Dosing at 4.0 mg is planned but has not yet begun. SD-101 has been administered to 5 patients with NHL who had progressive disease after an allogeneic bone marrow transplant in an ongoing investigator sponsored trial (Stanford University Medical Center, IND 111985). Three patients received 3 weekly intratumoral doses of SD-101 0.3 mg and 2 patients received 3 weekly intratumoral doses of SD-101 1.0 mg. One unrelated SAE of Klebsiella bacteremia was reported in a patient who received SD-101 1.0 mg. No other AEs have been reported (Dynavax personal communication with investigator). The recommended dose of SD-101 for combination trials is 4mg.

2.6 Safety Considerations

As monotherapy the AE of SD-101 include headache, injection site reaction, transient flu-like illness, myalgia, and pyrexia. As monotherapy the most common AE in 149 patients treated with epacadostat were (% ≥ Grade 3): diarrhea (0%), nausea (3.4%), vomiting (2.7%), asthenia (0%), fatigue (4%), elevated AST/ALT (1.3%), arthralgia (0%), pruritus (0%) and skin rash (1.3%). Both agents are well tolerated as single agents. The toxicity profile of these agents demonstrates minimal risk of overlapping toxicity. It is possible that the skin rash associated with epacadostat could exacerbate the injection site reaction induced by SD-101 or that arthralgia associated with epacadostat could exacerbate the flu-like symptoms and myalgia induced by SD-101.

Given the minimal risk of overlapping toxicity and the tolerability of the agents as monotherapy, we anticipate that SD-101 will be well tolerated in combination with

epacadostat. Furthermore, the local intralesional administration of SD-101 is likely to limit the potential for systemic interactions with epacadostat. Likewise, both classes of agents are likely to be well tolerated in combination with radiotherapy given the preclinical and clinical data outlined in section 2.2. This is confirmed in our pre-clinical mouse and large animal canine studies that demonstrate minimal toxicity when combining these therapies. Additionally, epacadostat has demonstrated safety and little evidence of potentiating toxicity in trials with other immunotherapy agents which are more toxic than SD-101. In 543 patients treated with epacadostat and anti-PD-1 combination therapy the most common AE were (% ≥ Grade 3): adrenal insufficiency (0.2%), hypothyroidism (0%), diarrhea (1.5%), nausea (1.7%), vomiting (1.8%), asthenia (1.3%), fatigue (2%), elevated AST/ALT (1.7%), arthralgia (0.3%), pneumonitis (0.2%), pruritus (0.6%) and skin rash (2.9%). Similar results are observed in 124 patients treated in combination with anti-PD-L1 therapy, and 32 patients treated with a JAK inhibitor.

In this trial we will initiate study with the 300mg bid dosing of epacadostat. As monotherapy the MTD of epacadostat was not reached at 600 mg bid. This 300mg bid dose is currently being tested in other phase II studies of epacadostat in combination with immunotherapy. The safety profile for the 300mg bid dose of epacadostat in combination with pembrolizumab in the Phase I/II study (INCB24360-202) did not exceed the MTD in that study. While there was a higher incidence of grade 3 rash in the 300mg bid cohort compared to the 100mg bid cohort, these did not qualify as protocol-specified DLTs. The dose of 300mg epacadostat in combination with pembrolizumab is currently under study in all current protocol. One exception is the dose combination of 100mg bid epacadostat plus pembrolizumab for the Phase III melanoma study (INCB24360-301) which is based upon a benefit/risk assessment made specifically in melanoma in collaboration with Merck. In INCB24360-202, there was evidence of improved efficacy in melanoma subjects at all doses of epacadostat of from 50 to 300mg bid. Given that melanoma is an immunotherapy responsive tumor, and lower doses of epacadostat appeared to have similar activity, the decision was made to take the 100mg bid dose combination forward because of the lower incidence of dose interruptions and dose reductions compared to the 300mg bid dose. However, in other tumor types, which appear to demonstrate more resistance to known immunotherapies, greater target coverage for inhibition of IDO1 may be necessary. Our PK/PD modelling suggests that doses of 100mg bid epacadostat achieve an average IC50 at trough in most patients. At 300mg bid, epacadostat achieves target inhibition above the IC90 at trough. The greater target inhibition necessary in more resistant tumors balances benefit/risk in favor of the higher epacadostat dose combination given that the dose does not exceed the MTD.

This trial will follow a dose de-escalation design. This design is chosen based on a risk/benefit analysis. The safety of the 300mg bid dose of epacadostat in combination with SD-101 is uncertain. However, based on the limited toxicity of these agents as monotherapy; the non-

overlapping toxicity profile of these agents; the limited systemic effects of SD-101 due to local intralesional administration; the tolerability of this dose of epacadostat in combination with other, more toxic, immunotherapies; the lack of evidence that epacadostat potentiates the toxicity of other immunotherapies; and the limited toxicity of this combination observed in preclinical mouse and large animal studies; we believe that the potential for toxicity is low. Our analysis of the low potential for toxicity at the 300mg bid dose coupled with the potential benefit of this dose in terms of target inhibition supports the design of a de-escalation study initiated at the 300mg bid dose of epacadostat as the most ethical design by limiting treating patients at a lower dose which may be less effective when the dose with superior target inhibition is likely to be tolerated.

2.7 Biomarkers

One of the major shortcomings of immunotherapy trials has been the lack of in depth correlative studies to help identify the mechanism of action, identify biomarkers of response, and explain the mechanisms governing treatment response or failure. To address this we plan to perform in depth immunological analysis of patient blood and tumor samples. This study incorporates serial tissues samples pre-treatment (during needle placement for the first SD-101 injection), during ERS therapy and at progression (optional). The design of this study allows us to compare immune mechanisms pre- to post-therapy.

Tumor PD-L1 expression has been linked to response rates of PD-1 checkpoint blockade [49]. Pre-clinical data suggests that radiotherapy may upregulate intratumoral PD-L1 expression [50] but little is known about the dose response of these effects. Additionally little is known about how the pattern of expression (i.e tumor cells vs. infiltrating immune cells) affects response. Data presented at ASCO and SITC indicate that durvalumab monotherapy response rates in NSCLC are 27% in PD-L1 positive tumors and 5% in PD-L1 negative tumors. TILs and a T-cell inflamed phenotype have been linked with response to CTLA-4 checkpoint blockade in melanoma [51, 52]. Exclusion of T-cells in the tumor microenvironment has also been linked with lack of response to checkpoint inhibition [53] with down-regulation of CCL4 mediated dendritic cell recruitment as one potential mechanism [53]. RT has been demonstrated to induce TILs [54] and may potentially overcome this mechanism of resistance to checkpoint blockade. Our unpublished data suggests that RT can induce CCL4 expression and increase TILs. Whether PD-L1 expression or the presence of TILs is important for response to epacadostat or SD-101 is unknown.

Mutational burden and antigenic load are thought to represent a surrogate for tumor antigenicity and have been linked with response to checkpoint blockade in NSCLC [55]. Whether mutational load is true indicator of tumor antigenicity and how this correlates with response to epacadostat or SD-101 is unknown.

Our previous studies demonstrate that upregulation of IDO and intratumoral Tregs are a mechanism of resistance to radiotherapy + CpG immunotherapy. Thus examining IDO levels and the presence of intratumoral Tregs will be critical for testing our hypothesis.

A growing body of evidence suggests that the gut microbiome is an important contributor to the overall immune and inflammatory status of an individual. The intestinal flora can produce bioactive molecules such as short chain fatty acids and tryptophan metabolites which can have profound effects on immune responses. The microbiome could influence the outcome of immunotherapy and play a role in regulating the anti-cancer immune response.

3. STUDY DESIGN

This is a phase I/II study that will use a standard 3 + 3 design followed by a Simon-two stage patient expansion as illustrated in the schema. For the phase I portion the primary endpoint is to determine the maximum tolerated dose (MTD). For the phase II portion the primary endpoint is safety and toxicity. Safety and toxicity will be evaluated using CTCAE v4.03. The secondary endpoint and the endpoint used for the Simon-two stage design is the disease control rate (DCR) defined as complete response + partial response + stable disease (CD+PR+SD). This endpoint is being used because several studies have demonstrated that patients without response to immunotherapy can still have long term disease stability which is of clinical benefit. Determining treatment tolerability (as defined in section 6.6) is also a secondary endpoint. Exploratory endpoints include objective response rate (ORR), progression free survival (PFS), overall survival (OS), and correlative studies.

Up to four dose levels of epacadostat will be evaluated: 50 mg bid, 100 mg bid, 200 mg bid and 300 mg bid. These 4 dose levels were selected based on the clinical data described above. We have chosen 300 mg bid as the starting dose level given the existing safety data for this dose and the safe use of this dose in use with other immunotherapy combinations. There is a -1, -2 and -3 dose level. If dose level -3 is not tolerated the study will be halted and modified after discussion with principal investigators and study sponsors. Epacadostat will be administered orally twice daily until disease progression. The expansion phase will be conducted using the MTD defined as the highest dose at which no more than one of six patients develops a DLT or Dose Level 1 if the MTD is not reached.

Radiotherapy will be delivered to the treatment lesion during the first week of ERS therapy using one of the following three standard-of-care palliative fractionation regimens: 8 Gy x 3 fractions, 4 Gy x 5 fractions, or 2 Gy x 2 fractions (cohort 2 only). Fractions may be delivered on consecutive or every other day but must be completed during week 1. The treatment lesion may be in a previously irradiated field as long as previous radiotherapy to that field was delivered > 6 months ago and re-irradiation is deemed safe.

Four milligrams of SD-101 will be delivered into the treatment lesion by intralesional injection on days 1, 8, 15, 22, and 29. On Day 1 biopsy will precede intralesional injection, RT, or epacadostat. Intralesional injections will be performed by palpation of the lesion or under ultrasound or CT guidance as indicated. For patients with a visceral treatment lesion Day 22 and 29 injections are optional. A visceral lesion can be used as the treatment lesion only if considered safe for serial intralesional injections. Visceral treatment lesions must be easily identified and accessible for image guided needle placement, carry minimal risk of bleeding or infection, and minimal risk of damage to the organ or surrounding tissues. For example, liver or adrenal lesions may be suitable candidate treatment lesions whereas lesions in the lung, bowel, or heart would not be.

A DLT is defined as any of the following that occur during the 30 day DLT period: grade $\geq$ 4 injection site reaction OR $\geq$ grade 3 treatment-related non-hematologic toxicity (excluding injection site reactions) OR AST/ALT > 3 x ULN with bilirubin > 2 X ULN, OR pneumonitis that requires holding treatment > 14 days. All toxicities at least possibly related to the investigational regimen will be considered treatment-related. Grade 3 rash will not be included as a DLT if there is no desquamation, no mucosal involvement, if it resolves without systemic corticosteroids by the next scheduled dose of epacadostat or 14 days, whichever is longer, and epacadostat dose intensity is maintained at 75% of planned dose during DLT period (i.e < 8 days of dose interruption). If epacadostat dose intensity cannot be maintained at 75% of planned dose during DLT period as a result of toxicity of any grade this will also be deemed a dose limiting toxicity.

Table 1 describes the standard dosing rules that will be followed.

Table 1. Dose De-Escalation Rules

Number of Patients with DLT at a Given Dose Level	De-Escalation Decision Rule
0 or 1 out of 3	Enter 3 additional patients at the dose level.
$\geq$2 out of 3 or 6	De-escalate the dose to the next lower level and accrue 3 patients.
<2 out of 6 at the highest dose level	This is the recommended phase 2 dose.

DLT=dose limiting toxicity

Patients will be monitored weekly during a 30-day DLT period and every 30 days thereafter or more frequently if needed. All patients on active treatment will be discussed at weekly conferences of the trial investigators. Per Cancer Center guidelines, a trial cannot proceed to the next dose level until a DLT meeting is conducted to comprehensively review all toxicity data and approve the dose escalation. Preliminary efficacy as determined by ARR, ORR, DCR, OS and DFS will be assessed every 60 days. The patient will remain on protocol

treatment until progression as determined by irRECIST, treatment is no longer tolerated, or the patient has completed 12 months of treatment. Patients on active treatment at 12 months may continue to receive epacadostat if they are tolerating therapy and are free from disease progression by irRECIST criteria. If patients have an objective response and stop treatment after 12 months and then have PD, they can be considered for re-treatement at the discretion of the study PI. After study completion PFS, OS and long-term toxicity data will continue to be collected every 3 months during routine standard of care visits.

4. STUDY POPULATION

Patients will be recruited from the UC Davis Cancer Center. All patients will be registered at the UC Davis facility after consultation with Dr. Daly. Patients will be identified through the various clinics at UC Davis, at the UC Davis multidisciplinary tumor boards, and the UC Davis Comprehensive Cancer Center (UCDCC) Phase I clinic. Based on the inclusion of numerous histologies and the high volume of patients with advanced disease treated at the UCDCC we conservatively project a 36 month accrual period.

4.1 Inclusion Criteria

1. Adults $\geq$18 years of age with histologically proven solid malignancy, high-grade lymphoma or low-grade lymphoma.
2. Patients with incurable, advanced or metastatic disease refractory to at least one previous line of therapy.
3. ECOG (Eastern Cooperative Oncology Group) performance status score of 0 – 2 (Appendix 1).
4. Presence of a candidate treatment lesion (subcutaneous, nodal, or visceral) accessible and safe for radiotherapy and serial intralesional injections as specified by the protocol.
5. Presence of at least one target lesion (distinct from treatment lesion and outside of treatment lesion radiation field) evaluable for response by irRECIST.
6. 14 day wash-out period from any previous chemotherapy, targeted therapy or radiotherapy, 21 day washout period from previous immunotherapy.
7. Life expectancy $\geq$ 6 months.
8. Adequate hematologic and end organ function, defined by the following laboratory results obtained within 14 days of the first study treatment:
    - ANC > 1500 cells/ul; WBC count > 2500/uL; Platelet count > 50,000/uL; Hemoglobin > 9 g/dL
9. Liver function tests meeting one of the following criteria:
    a. AST and ALT < 2.5 x ULN with alkaline phosphatase $\leq$ 2.5 x ULN OR

b. AST and ALT ≤ 1.5 x ULN, with alkaline phosphatase > 2.5 x ULN

c. Serum bilirubin ≤ 1.0 x ULN. Direct bili ≤ 40% if total bili > ULN in patients with Gilbert's syndrome.

10. INR and aPTT < 1.5 x ULN.

11. Serum Cr ≤ 1.5 X ULN or CrCl ≥ 50 ml/min.

12. No active auto-immune disease and not on therapy for auto-immune disease. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone are eligible. Patients who have adrenal insufficiency and hypophysitis from prior immunotherapy if they are on stable medical replacement doses are eligible.

13. No other active malignancy.

14. Patients with controlled Type 1 diabetes mellitus on a stable insulin regimen are eligible.

15. For female patients of childbearing potential and male patients with partners of childbearing potential agreement (by patient and/or partner) to use highly effective form(s) of contraception (i.e., one that results in a low failure rate [<1% per year] when used consistently and correctly) and to continue its use for 6 months after trial completion.

16. Signed informed consent.

17. At least 9 months from stem cell transplant with no active graft versus host disease.

18. Ability to comply with the protocol.

4.2 Exclusion Criteria

1. Uncontrolled concomitant disease that in the opinion of the investigator would interfere with the patient's safety or compliance on trial.

2. Significant cardiovascular disease (NYHA Class II or greater); myocardial infarction within 3 month prior to randomization, unstable arrhythmias, unstable angina or a patient with a known LVEF (Left Ventricular Ejection Fraction) < 40%

3. Severe infection that in the opinion of the investigator would interfere with the patients safety or compliance on trial within 2 weeks prior to enrollment. Oral or IV antibiotics within 2 weeks or 5 half-lives prior to enrollment.

4. Active tuberculosis

5. History of severe autoimmune disease that in the opinion of the investigator would interfere with patient safety or compliance on trial.

6. Positive for Human Immunodeficiency Virus (HIV), Hepatitis B (Hepatitis B Surface Antigen [HBsAg] reactive), or Hepatitis C virus (Hepatitis C Virus Ribonucleic Acid [HCV RNA] (qualitative) is detected)
7. Previous treatment with epacadostat, SD-101, or any other IDO inhibitor or CpG molecule.
8. Treatment with systemic corticosteroids or other systemic immunosuppressive medications within past 4 weeks or 5 half-lives whichever is shorter. Use of inhaled or topical steroids or systemic corticosteroids < 10 mg/ day of prednisone (or equivalent) is permitted.
9. Pregnant and/or lactating women.
10. Evidence of active interstitial lung disease or active non-infectious pneumonitis
11. Receipt of live attenuated vaccine within 30 days before the first dose of study treatment.
12. Use of any UGT1A9 inhibitor while on active study treatment, including the following: diclofenac, imipramine, ketoconazole, mefenamic acid, and probenecid.
13. Known allergy or reaction to any component of either study drug formulation.
14. Subjects receiving Monoamine Oxidase Inhibitors (MAOIs) or drug which has significant MAOI activity (meperidine, linezolid, methylene blue) from 21 days prior to Day 1 through 2 weeks after the final dose of epacadostat has been administered.
15. Any history of Serotonin Syndrome (SS) after receiving serotonergic drugs.
16. Known contraindications to radiotherapy including but not limited to radiation sensitivity syndromes such as xeroderma pigmentosum and ataxia telangiectasia mutated.

5. TREATMENT PLAN

Table 2. Treatment Plan

Agent	Dose	Route	Frequency
Epacadostat	50 - 300 mg BID	Oral	BID throughout study period.
Radiation	4 - 24 Gy	External beam	3 fractions of 8 Gy, 5 fractions of 4 Gy, or 2 fractions of 2 Gy (cohort 2 only), delivered 12–96 hours apart during the first week of therapy.
SD-101	4 mg	Intratumoral	5 total doses 1 x weekly on days 1,8,15, 22, and 29 (Day 22 and 29 optional for visceral treatment lesions). First dose to be delivered prior to radiotherapy.

5.1 Epacadostat

5.1.1 Dosage and Administration

Epacadostat will be administered at the MTD (50 – 300mg) orally BID throughout the study period. Subjects will take their dose of epacadostat in the morning and evening, approximately 12 hours apart without regard to food. If the morning or evening dose is missed by more than 4 hours, that dose should be skipped and the next scheduled dose should be taken at the usual time. All BID doses will be taken in the morning and evening, approximately 12 hours apart.

5.1.2 Formulation, Packaging, and Handling

Epacadostat is formulated as an immediate release tablet in 2 strengths (25 mg and 100 mg) tablets packaged in high-density polyethylene bottles. The tablets contain the active drug (epacadostat) along with commonly used compendial excipients (lactose monohydrate, microcrystalline cellulose, povidone, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate). Epacadostat drug product should be stored at ambient conditions (15°C–30°C or 59°F – 86°F).

5.1.3 Disposal and Destruction

Drug supply will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to Incyte with the appropriate documentation. The site's method of drug supply destruction must be agreed upon by Incyte.

Accurate records of all investigational product received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Log.

5.2 SD-101

5.2.1 Dosage, Administration, and Compliance

SD-101 will be administered as a 4 mg dose to the treatment lesion through intralesional needle placement. Needle placement will be performed by palpation, ultrasound, or computed tomography guidance as indicated. 5 intralesional injections will be administered over a 5 week period on days 1, 8, 15, 22, and 29. The final two injections are optional for patients with visceral treatment lesions.

5.2.2 Formulation, Packaging, and Handling

SD-101 is supplied in single use vials. The sterile, preservative-free drug is supplied at a concentration of 16 mg/mL. SD-101 contains no preservatives and must be stored under refrigerated conditions (2°C to 8°C). SD-101 is not to be frozen. Available stability data indicate that SD-101 Drug Product (5 mg/mL) is stable for at least 65 months when stored refrigerated at 2°C to 8°C, the recommended storage condition. SD-101 will be brought to room temperature and administered at a 4 mg dose according to the clinical trial protocol.

5.2.3. Preparation of SD-101 4 mg/mL Solution

Withdraw 1.5 mL of commercially sourced NaCl 0.9% diluent using a 3 mL syringe and transfer into an empty sterile 5 mL vial. Withdraw 0.5 mL of SD-101 (16 mg/mL) injectable solution from the IP vial in a 1 mL syringe using a 25 G, 1 ½" needle. Transfer SD-101 to the sterile vial containing 1.5 mL of NaCl 0.9%. To mix the solution, gently invert the vial 10 times. The sterile vial will contain a 4 mg/mL solution of SD-101. Using a 20-25 G needle, withdraw 1 mL of the diluted SD-101 (4 mg/mL) into a 3 mL syringe for administration of a 4 mg fixed dose of SD-101. A 25-30 G needle must be used to administer the dose of SD-101. Compounded preparations must be administered within 8 hours of making the dilution.

5.2.4 Disposal and Destruction

Drug supply will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to Dynavax with the appropriate documentation. The site's method of drug supply destruction must be agreed upon by Dynavax.

Accurate records of all investigational product received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Log.

5.3 Radiotherapy

5.3.1 Dose Specifications and Treatment Delivery

Radiotherapy will be delivered as 24 Gy over 3 fractions of 8 Gy, 20 Gy delivered over 5 fractions of 4 Gy, or 4 Gy delivered over 2 fractions of 2 Gy (for cohort 2 only). There should be a minimum of 12 hours and a maximum of 96 hours between treatments. All treatments must commence on day 1 after intralesional injection of SD-101 and must be completed within study week 1. Corticosteroid premedication is not permitted. Analgesic premedication to avoid general discomfort during long treatment durations is recommended when appropriate. The dose per fraction is to be prescribed such that the entire planning treatment volume (PTV) is encompassed by 95% of the prescription dose.

5.3.2 Technical Factors

Only photon (x-ray) beams with photon energies 4-15 MV or electron beams with electron energies of 6-12 MeV will be allowed.

5.3.3 Localization, Simulation, and Immobilization

Patients will be positioned in a stable position capable of allowing accurate reproducibility of the target position from treatment to treatment. Patient immobilization must be reliable enough to ensure that the gross tumor volume (GTV) does not deviate beyond the confines of the PTV as with any significant probability (i.e., < 5%). Patients will undergo an imaging study (electron portal imaging, conebeam computed tomography or Megavoltage computed

tomography) immediately prior to treatment to ensure proper alignment of the geometric center (i.e., isocenter) of the simulated fields.

5.3.4 Target Volumes

5.3.4.1 Image Acquisition

Computed tomography will be used for targeting and treatment planning. IV contrast is encouraged when its use will enhance target delineation but is not required. Axial acquisitions with gantry 0 degrees will be required with spacing ≤ 3.0 mm between scans in the region of the tumor.

5.3.4.2 Target Volume

The treatment lesion will be outlined and designated the gross tumor volume (GTV). No additional clinical target volume (CTV) margin for microscopic spread will be added. Depending on the stability and reproducibility of patient setup an additional margin of 0.5 – 3 cm will be added to the GTV to constitute the PTV.

5.3.4.3 Technique and Dose Calculations

Conformal treatment approaches including 3D conformal radiotherapy using static, preferably non-coplanar fields; intensity modulated radiotherapy (IMRT), Volume Modulated Arc therapy (VMAT), Dynamic Conformal Arc Radiation Therapy (DCART), and helical tomotherapy are acceptable. Isodose lines covering the PTV must be >= 95% of the prescribed dose. When IV and/or oral contrast are used, contrast densities should be overridden in the planning process. Tissue density heterogeneity correction is required for lung tumors. Superposition/convolution dose algorithms are preferred.

All radiotherapy plans will be centrally reviewed by Dr. Daly prior to delivery of the first fraction.

5.3.5 Organs at Risk

5.3.5.1 Defining Organs at Risk

Palliative radiotherapy is delivered as standard of care to a subcutaneous, nodal, or visceral treatment lesion. The anatomic location of the treatment lesion is undefined and left to the discretion of the treating physician. Therefore, a designated set of organs at risk to be included in each radiotherapy treatment plan cannot be defined. Organs at risk will be defined by the treating radiation oncologist if visible within the axial slices covered by the PTV. Organs at risk to be contoured include but are not limited to: optic nerves, globes, cochlea, brainstem, spinal cord, cauda equina, sacral plexus, esophagus, brachial plexus, heart, great vessels, trachea and proximal bronchial tree, rib, skin, stomach, duodenum, jejunum/ileum, colon, rectum, bladder, penile bulb, femoral heads, renal hilum, lungs, liver, and kidneys. These contours should be

labeled according Standard Naming Conventions listed below in parentheses as per https://www.rtog.org/CoreLab/StandardizedNamingConventions.aspx. Organs at risk should be defined using existing guidelines and atlases available at: https://www.rtog.org/CoreLab/ContouringAtlases.aspx. If necessary, the assistance of a board certified radiologist should be sought to aid in contouring. Guidelines for defining commonly encountered organs at risk are described below.

- Spinal cord (Spinalcord): The spinal cord will be contoured based on the bony limits of the spinal canal. The spinal cord should be contoured starting at least 10 cm above the superior extent of the PTV and continuing on every CT slice to at least 10 below the inferior extent of the PTV.

- Brachial plexus (BrachialPlex_L and BrachialPlex_R): The defined ipsilateral brachial plexus originates from the spinal nerves exiting the neuroforamina on the involved side from around C5 to T2. However, for the purposes of this protocol, only the major trunks of the brachial plexus will be contoured using the subclavian and axillary vessels as a surrogate for identifying the location of the brachial plexus. This neurovascular complex will be contoured starting proximally at the bifurcation of the brachiocephalic trunk into the jugular/subclavian veins (or carotid/subclavian arteries) and following along the route of the subclavian vein to the axillary vein ending after the neurovascular structures cross the second rib.

- Esophagus (Esophagus): The esophagus will be contoured using mediastinal windowing on CT to correspond to the mucosal, submucosa, and all muscular layers out to the fatty adventitia. The esophagus should be contoured starting at least 10 cm above the superior extent of the PTV and continuing on every CT slice to at least 10 below the inferior extent of the PTV and ideally from the post-cricoid space to the GE junction.

- Great Vessels (GreatVessels): The great vessels (aorta and vena cava, not the pulmonary artery or vein) will be contoured using mediastinal windowing on CT to correspond to the vascular wall and all muscular layers out to the fatty adventitia. The great vessel should be contoured starting at least 10 cm above the superior extent of the PTV and continuing on every CT slice to at least 10 cm below the inferior extent of the PTV. For right sided tumors, the vena cava will be contoured, and for left sided tumors, the aorta will be contoured.

- Heart/pericardium (Heart): The heart will be contoured along with the pericardial sac. The superior aspect (or base) for purposes of contouring will begin at the level of the inferior aspect of the aortic arch (aortopulmonary window) and extend inferiorly to the apex of the heart.

- Trachea and proximal bronchial tree (Trachea, BronchialTree): The trachea and proximal bronchial tree including the mainstem and lobar bronchi including trachea, the carina, the right and left mainstem bronchi, the right and left upper lobe bronchi, the intermedius bronchus, the right middle lobe bronchus, the lingular bronchus, and the right and left lower lobe bronchito the bifurcation of the first segmental airways will be contoured using mediastinal windows on CT to

correspond to the mucosal, submucosa and cartilage rings and airway channels associated with these structures.

- Skin (SkinOAR): The skin will be defined as the outer 0.5 cm of the body surface. As such it is a rind of uniform thickness (0.5 cm) which envelopes the entire body in the axial planes. The cranial and caudal surface of the superior and inferior limits of the planning CT should not be contoured as skin unless skin is actually present in these locations (e.g., the scalp on the top of the head).

- Stomach (Stomach): The entire stomach and its contents should be contoured as a single structure as a continuation of the esophagus and ending at the first part of the duodenum.

- Duodenum (Duodenum): The wall and contents of the 1st, 2nd, and 3rd parts of the duodenum will be contoured as one structure beginning where the stomach ends and finishing as the superior mesenteric artery crosses over the third part of the duodenum

- Jejunum/ilieum (Smallbowel): Small bowel from end of duodenum to the ileocecal area.

- Large Bowel (Largebowel): From the ileocecal area to include the ascending, transverse, descending and sigmoid colon as one structure.

- Renal hilum/vascular trunk: The renal artery and vein from the renal cortex to the great vessels.

- Liver (Liver): The entire live minus the GTV

- Kidneys (Kidney_L and Kidney_R): Both the right and left kidney, excluding renal pelvis/collecting system, should be contoured in their entirety (the renal cortex)

- Lung (Lungs): Both the right and left lungs should be contoured as one structure. Contouring should be carried out using pulmonary windows. All inflated and collapsed lung should be contoured; however, gross tumor (GTV) and trachea/ipsilateral bronchus as defined above should not be included in this structure.

- Rectum: The muscular wall of the rectum should be contoured, extending from the anus to the rectosigmoid junction

- Femoral Heads: The right and left femoral heads extending to the lesser trochanter should be contoured separately

- Bladder: Outer muscular wall should be contoured

5.3.5.2 Organs at Risk Dose Constraints

Listed below are the maximum dose limits to a point or critical volume within organs at risk. Maximum point dose will be defined as the maximum dose to a 0.035 cc volume. These are absolute limits, and treatment delivery that exceeds these limits will constitute a major protocol violation. As outlined above other organs at risk may be defined by the treating physician based on the location of the treatment lesion and these organs should be constrained using standard accepted dose constraints. Radiotherapy will be delivered as 24 Gy over 3 fractions of 8 Gy, 20 Gy delivered over 5 fractions of 4 Gy, or 4 Gy delivered over 2 fractions of 2 Gy and the constraints will vary based on the prescribed dose. In all cases the maximum hotspot for a given plan should not exceed 120% of the prescribed dose.For 4 Gy delivered over 2 fractions of 2 Gy there are no dose constraints for organs at risk.

For 20 Gy delivered over 5 fractions of 4 Gy dose constraint for the optic nerves, globes, cochlea, brainstem, and spinal cord is a max point dose of 22 Gy (4.4 Gy / fx). For the lung (right and left) 1500cc should receive less than 12.5 Gy. For the liver 700cc should receive less than 15 Gy. For the kidneys (right and left) 200c should receive less than 15 Gy. All other organs at risk should be constrained to below 120% of the prescribed dose.

For 24 Gy delivered over 3 fractions of 8 Gy the dose constraints for organs at risk are listed in the Table 3. Recent studies have shown that the rib and chest wall in proximity to the treated lesion may represent an organ at risk for complication such as chest wall pain and rib fracture. While target coverage should not be compromised to limit dose to the rib/chest wall and formal constraint is not provided, every effort should be made to minimize dose and hostpots to this organ at risk.

Table 3. Critical Organs at Risk Dose-Volume Limits for 24 Gy over 3 fractions

Structure	Volume (mL)	Volume Max (Gy)	Max Point Dose (Gy)	Volumetric Constraint
Optic nerves			15	
Globes			15	
Cochlea			18	
Brainstem			18	
Spinal cord	<0.25	17	18	
Sacral Plexus	<5	21.9	24	
Brachial plexus	<3	20.4	24	

Cauda equina	<5	21.9	24	
Esophagus	<5	21	27	
Great Vessels	-	-	25.2 (105% of Rx dose)	
Heart/pericardium	<15	24	25.2 (105% of Rx dose)	
Trachea and ipsilateral bronchus	<4	15	25.2 (105% of Rx dose)	
Skin			28.8	
Stomach	<10	21	24	
Duodenum	<5	15	22.2	
Jejunum/ilieum	<5	16.2	25.2 (105% of Rx dose)	
Colon/Rectum	<20	24	28.2 (105% of Rx dose)	
Bladder	<15	16.8	28.2	
Renal Hilum	<15	19.5	-	
Femoral Heads	<10	21.9		
Liver	700mL spared from volume max	15		
Kidneys	200mL spared from volume max	14.4		
Lung (left and right)	1500mL spared from volume max	10.5		V20<10%

6. GENERAL PLAN TO MANAGE SAFETY CONCERNS

Measures will be taken to ensure the safety of patients participating in this trial, including the use of stringent inclusion and exclusion criteria (see Sections 4.1 and 4.2) and close monitoring (as indicated below and in the study calendar).

6.1 Eligibility Criteria

Eligibility criteria were selected to guard the safety of patients in this trial. Results from the nonclinical toxicology studies as well as the nonclinical/clinical data from other studies were taken into account.

6.2 Monitoring

Safety will be evaluated in this study through the monitoring of all serious and non-serious AEs, defined and graded according to NCI CTCAE v4.03. Patients will be assessed for safety (including laboratory values) according to the Study Calendar. Patients will be followed for safety for 30 days following the last dose of study treatment or until receipt of another anticancer therapy, whichever comes first. General safety assessments will include serial interval histories, physical examinations, and specific laboratory studies, including serum chemistries and blood counts (see Study Calendar for the list and timing of study assessments). **All serious adverse events (SAEs) will be reported in an expedited fashion**. In addition, the investigators will review and evaluate observed AEs on a regular basis.

Patients who have an ongoing study treatment–related AE upon study completion or at discontinuation from the study will be followed until the event has resolved to baseline grade, the event is assessed by the investigator as stable, new anticancer treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or until it has been determined that study treatment or participation is not the cause of the AE.

6.3 Management of Specific Adverse Events

Toxicities associated or possibly associated with protocol treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, may be used to determine a possible immunogenic etiology.

Although most immune-related adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of protocol therapy may not have an immediate therapeutic effect and in severe cases, immune-related toxicities may require acute management with topical corticosteroids, systemic corticosteroids, mycophenolate, or TNF-α inhibitors.

6.4 Management of Adverse Events from Immunotherapy

The primary approach to Grade 1-2 immune-related adverse events is supportive and symptomatic care with continued protocol therapy; for higher grade immune-related adverse events, therapy should be held and oral/parental steroids administered. Recurrent Grade 2 immune-related adverse events may also mandate holding therapy or the use of steroids. In the case of all toxicities consideration for benefit/risk balance should be made by the investigator, with consideration of the totality of information as it pertains to the nature of the toxicity and the degree of clinical benefit a given patient may be experiencing prior to further administration of ERS therapy. ERS therapy should be permanently discontinued in patients with life-threatening immune related AEs (irAE). Management of AE by grade (Table 3) and symptomatic management of specific AEs (Table 4) are outlined below.

Table 4. General Management of AE by Grade (refer to Table 4 for specific AEs)

irAE Toxicity Grade	Withhold/ Discontinue	Action Taken With Respect to Epacadostat	Supportive Care (see also Table 4)
Grade 1	No action.	Not applicable.	Provide symptomatic treatment.
Grade 2	May withhold study treatment per investigator's discretion.	If AE resolves within 30 days, subject may restart at the same dose and schedule for epacadostat. For an AE that does not resolve within 30 days, consider reducing epacadostat 1 dose level.	Consider systemic corticosteroids in addition to appropriate symptomatic treatment.
Grade 3	Withhold study treatment until AE resolves to ≤ Grade 2. Discontinue if study treatment cannot be resumed within 30 days.	Restart epacadostat at reduced dose level except in the case of Grade 3 rash that resolves without oral steroids. If AE does not resolve to < Grade 2 within 30 days after re-initiating study treatment or progresses again to grade 3 after initiating study treatment reduce epacadostat 1 dose level. Discontinue therapy for grade 3 pnuemonitis.	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. May use 1-2 mg/kg prednisone or equivalent per day. Steroid taper should be considered once symptoms improve to ≤ Grade 2 and tapered over at least 4 weeks in most cases.
Grade 4	Withhold study treatment until AE resolves to ≤ Grade 2. Discontinue if study treatment cannot be resumed within 30 days.	Restart epacadostat at reduced dose level if the AE resolves to ≤ Grade 2or baseline. If there is recurrence of a Grade 3/4 AE with reduced dose of epacadostat, then discontinue participation in the study.	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. May use 1-2 mg/kg prednisone or equivalent per day. Steroid taper should be considered once symptoms improve to ≤ Grade 2 and tapered over at least 4 weeks in most cases.

Table 4: Specific Management of Adverse Events

Adverse Event	CTCAE v4.03 Grade	Recommended Symptom Specific Management (to be used at discretion of treating physician)
Injection site reaction	1-3	Administer 325-650 mg acetaminophen po every 4-6 hours prn. Note: Maximum cumulative daily dose of acetaminophen is 4 grams daily due to risk of severe liver toxicity.
Injection site reaction	4	Hold study treatment until injection site reaction resolves
Rash	1-2	Supportive care including topical emollients, sun protection, consider topical steroids
Rash	3	Interrupt epacadostat, use topical corticosteroids, consider oral corticosteroids. When rash ≤ grade 1, taper steroids if used, then restart at reduced dose. If only topical steroids used, can restart at same or reduced dose when ≤ grade 1..
Rash	4	Interrupt epacadostat and start oral steroids. Continue until ≤ grade 1 and taper steroids. Once steroids ≤ 10mg/day, restart at reduced dose
Flu-like symptoms	1-3	Administer 325-650 mg acetaminophen po every 4-6 hours prn. Note: Maximum cumulative daily dose of acetaminophen is 4 grams daily due to risk of severe liver toxicity.
Headache	1-3	Administer 325-650 mg acetaminophen po every 4-6 hours prn. Note: Maximum cumulative daily dose of acetaminophen is 4 grams daily due to risk of severe liver toxicity.
Nausea/vomiting	1 or 2	Prescribe antiemetics per treating physician's recommendation
Nausea/vomiting	3 or 4	Interrupt study treatment. Prescribe antiemetics per treating physician's recommendation. Fluid and electrolytes should be substituted via IV infusion if indicated. When nausea/vomitting resolves to ≤ Grade 2 restart epacadostat at a reduced dose level.
Diarrhea/colitis	1	Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood, or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). Continue treatment with epacadostat, and initiate supportive care measures, which include drinking liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. An antidiarrheal can be started.
	2	Interrupt study treatment if indicated, and initiate supportive care measures, which include drinking liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. An antidiarrheal should be started. When diarrhea resolves to baseline, restart epacadostat at the same dose.

Adverse Event	CTCAE v4.03 Grade	Recommended Symptom Specific Management (to be used at discretion of treating physician)
	3 or 4	Interrupt study treatment. When diarrhea resolves to baseline, restart epacadostat at a reduced dose. Monitor subjects for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, mucus or blood in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic subjects, rule out infectious etiologies and consider endoscopic evaluation for persistent or severe symptoms. For recurrent or persistent Grade 3 or 4 diarrhea, consider further dose reduction of epacadostat, or study treatment discontinuation.
Pneumonitis	2	Interrupt study drug and initiate systemic corticosteroids. Taper as necessary. May return to study treatment if condition improves to ≤ Grade 1. Permanently discontinue if toxicity does not resolve within 12 weeks of last dose or if subject shows inability to reduce corticosteroid to ≤ 10 mg prednisone or equivalent per day within 12 weeks.
	3 or 4	Permanently discontinue study drug. Immediately treat with intravenous corticosteroids. Administer additional anti-inflammatory measures, as needed. Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.
Type I diabetes mellitus (TIDM; if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)	3 or 4	Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria. Evaluate subjects with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.
Hypophysitis	2 or 3	Treat with oral corticosteroids. When symptoms improve to ≤ Grade 1, 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.
	4	Discontinue study drug. Treat with an initial dose of IV corticosteroids followed with oral corticosteroids. When symptoms improve to ≤ Grade 1, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
Hyperthyroidism or hypothyroidism	2	Thyroid disorders can occur at any time during treatment. Monitor subjects 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. In hyperthyroidism, nonselective beta-blockers (eg, propranolol) are suggested as initial therapy. In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care.

Adverse Event	CTCAE v4.03 Grade	Recommended Symptom Specific Management (to be used at discretion of treating physician)
	3 or 4	In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care. In hyperthyroidism, treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to ≤ Grade 1, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
Hepatic	2	Monitor liver function tests more frequently until returned to baseline values (consider weekly or twice weekly if steroids are not initiated). Treat with IV or oral corticosteroids.
	3 or 4	Treat with intravenous corticosteroids. When liver chemistry tests improve to ≤ Grade 1, a steroid taper should be started and continued over no less than 4 weeks. For recurrent or persistent Grade 3 liver chemistry tests, consider further dose reduction of epacadostat (see Table 5 for epacadostat dose modifications), or study treatment discontinuation. For persistent Grade 4 liver chemistry tests, discontinue study treatment.
Hy's law case[a]	4	Permanently discontinue study therapy at the first occurrence of liver enzyme elevations meeting the criteria for Hy's law.
Renal failure or nephritis	2	Treat with oral corticosteroids.
	3 or 4	Treat with systemic corticosteroids. When severity of the event improves to ≤ Grade 1, steroid taper should be started and continued over no less than 4 weeks. For recurrent or persistent Grade 3 renal failures or nephritis, consider further dose reduction of epacadostat (see Table 5 for epacadostat dose modifications), or study treatment discontinuation. For persistent Grade 4 renal failure or nephritis, discontinue study treatment.

[a] Hy's law is defined as follows: 1. Aminotransferase elevation (ALT or AST) > 3 × ULN; 2. Total bilirubin > 2 × ULN, without initial findings of cholestasis (elevated serum ALP); 3. No other immediately apparent possible cause of aminotransferase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, liver metastases, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic. Permanently discontinue study therapy at the first occurrence of liver enzyme elevations meeting the criteria for Hy's law.

6.5 Management of Adverse Events Associated from Radiotherapy

Radiotherapy is delivered as a standard of care palliative regimen and radiotherapy related toxicities will be addressed using standard institutional practices. With palliative doses delivered in this trial we anticipate minimal adverse effects for the treatment of dermal, subcutaneous, nodal, or visceral lesions.

6.6 Guidelines for Dosage Modification and Treatment Interruption or Discontinuation

Dosing interruptions may be permitted in the case of medical/surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, subject vacation, and/or holidays). Subjects will be placed back on study therapy within 4 weeks of the scheduled interruption. The reason for interruption should be documented in the subject's study record.

Criteria for dose modification, treatment interruption or discontinuation are outlined in Table 3 and Table 4.

A dose of epacadostat may be held up to 30 days. Patients unable to resume epacadostat after 30 days due to toxicity will discontinue ERS therapy due to treatment intolerability. Epacadostat may be dose reduced for a given patient after the DLT window of phase 1 or at any time in phase 2. Criteria for dose reduction of epacadostat are outlined in Table 3 and Table 4. Dose levels of epacadostat for dose reductions are outlined in Table 5. The dose of epacadostat may not be reduced below 50 mg BID even if the MTD is determined to be 100 mg BID. Patients requiring dose reductions below 50 mg bid will discontinue ERS therapy due to treatment intolerability.

Table 5: Dose Modifications of Epacadostat

Dose level 1	Dose Level -1	Dose Level -2	Dose Level -3
300 mg BID	200 mg BID	100 mg BID	50 mg BID

If necessary, doses of SD-101 can be delayed up to 5 days, but must be given within the intended treatment week. If this is not possible, the dose will be skipped completely. Every attempt should be made to deliver at least 3 doses during the treatment period. If a dose is delayed, the following dose should be delivered during the next treatment week, a minimum of 5 days after the previously given dose. Subsequent doses in subsequent weeks should also be administered a minimum of 5 days after the previous dose. The dose may not be modified. If more than two consecutives doses are missed due to toxicity, the patient may continue ERS therapy, but will be labeled as having treatment intolerability.

The prescribed dose of radiotherapy can be reduced to no lower than 60% of the dose as specified per fraction in response to treatment related toxicity at the treatment lesion or prior to the onset of treatment to respect normal tissue tolerances as deemed necessary by the treating radiation oncologist. If a dose of radiotherapy is missed it can be administered later within the first week of therapy. Any radiotherapy fractions not delivered during the first week of therapy cannot be made up and those doses will be skipped. Patients unable to receive at least 60% of the prescribed radiotherapy dose due to treatment toxicity may continue ERS therapy but will be labeled as having treatment intolerability.

6.7 Treatment Tolerability

DLTs and any other treatment related adverse event requiring discontinuation of ERS therapy will be deemed treatment intolerability. Patients unable to resume epacadostat after 30 days due to toxicity will discontinue ERS therapy and will be labelled as having treatment intolerability. If more than two consecutives doses of SD-101 are missed due to toxicity the patient may continue ERS therapy but will be labeled as having treatment intolerability. Patients unable to receive at least 60% of the prescribed radiotherapy dose due to treatment toxicity may continue ERS therapy but will be labeled as having treatment intolerability. Epacadostat dose reductions will not be labelled as treatment intolerability but will be reported separately.

6.8 Management of 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 other study drugs 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

7. CONCOMITANT AND EXCLUDED THERAPIES

7.1 Concomitant Therapy

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including blood transfusions) administered during the study should be recorded.

Concomitant therapy includes any prescription medications or over-the-counter preparations used by a patient between the 7 days preceding the screening evaluation and the treatment discontinuation visit.

Patients who experience infusion-associated symptoms may be treated symptomatically with antipyretics (ibuprofen preferred), diphenhydramine, and/or cimetidine or another H2 receptor antagonist, as per standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g. supplemental oxygen and β_2-adrenergic agonists).

Systemic corticosteroids and TNFα inhibitors may attenuate potential beneficial immunologic effects of treatment but may be administered at the discretion of the treating physician. If feasible, alternatives to corticosteroids should be considered. Premedication may be administered for Cycles ≥ 2 at the discretion of the treating physician. The use of inhaled

corticosteroids and mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency is allowed. Megastrol administered as appetite stimulant is acceptable while the patient is enrolled in the study.

Patients who use oral contraceptives, hormone-replacement therapy, prophylactic or therapeutic anticoagulation therapy (such as low-molecular-weight heparin or warfarin at a stable dose level), or other allowed maintenance therapy should continue their use. Males and females of reproductive potential should use highly effective means of contraception.

7.2 Excluded Therapy

Any concomitant therapy intended for the treatment of cancer, whether health authority-approved or experimental, is prohibited. This includes but is not limited to the following:

- Chemotherapy, hormonal therapy, immunotherapy, radiotherapy, investigational agents, or herbal therapy
    - After day 29, certain forms of radiotherapy may be considered for palliation if patients are deriving benefit (e.g., treatment of known bony metastases); ERS administration should be continued during such palliative radiotherapy.

It is strongly recommended that:

- Traditional herbal medicines not be administered because the ingredients of many herbal medicines are not fully studied and their use may result in unanticipated drug-drug interactions that may cause, or confound assessment of, toxicity

Patients are not allowed to receive immunostimulatory agents, including but not limited to IFN-α, IFN-γ, or IL-2, during the entire study. These agents, in combination with study treatment, could potentially increase the risk for autoimmune conditions.

Patients should also not be receiving immunosuppressive medications, including but not limited to cyclophosphamide, azathioprine, methotrexate, and thalidomide. These agents could potentially alter the activity and the safety of ERS therapy. Systemic corticosteroids and anti-TNFα agents may attenuate potential beneficial immunologic effects of the ERS therapy but may be administered at the discretion of the treating physician and if needed to manage treatment toxicity per guidelines outlined in this protocol. If feasible, alternatives to these agents should be considered.

In addition, all patients (including those who discontinue the study early) should not receive other immunotherapy agents for at least 14 days after discontinuing study therapy.

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

- Any investigational medication other than the study drugs.
- Any chronic immunological-suppressive treatment for any reason. (**Note:** Inhaled or topical steroids are allowed, and systemic steroids at doses ≤10 mg/day prednisone or equivalents are allowed and immune suppressants are allowed for short-term treatment for immune toxicities or as prophylaxis for contrast allergy for imaging procedures.)
- 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 study treatment initiation 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.
- **Note – Propofol, when used for short-term sedation during surgical/biopsy procedures, is allowed. The epacadostat dose may be taken on the morning of the procedure, and the evening dose held following the procedure. Epacadostat may be resumed the next day*

Subjects 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.

7.3 Restricted Medications/Treatment

- Systemic steroids may be used at doses ≤ 10 mg/day prednisone or equivalents.
- Use of coumarin-based anticoagulants (eg, Coumadin) is discouraged. Low-dose Coumadin® (1 mg) is acceptable; however, doses that increase the INR are discouraged and will require dose modification. If an alternative to coumarin-based anticoagulants cannot be used, dose modifications of the Coumadin® may be needed. Based on the observed magnitude of epacadostat/warfarin PK interaction and PK/PD modeling results, for an epacadostat dose of 300 mg BID, the dose of warfarin should be reduced by approximately one-third after initiation of epacadostat administration based on approximately 30% to 40% reduction in S- and R-warfarin oral clearance values. Close INR monitoring is recommended for subjects on a stable dose of warfarin who are starting treatment with epacadostat. Based on PK/PD modeling, recommendations for warfarin dose modifications for subjects receiving other epacadostat doses, are summarized in Table 7 based on the INR prior to starting epacadostat.

Table 7: Warfarin dose modifications with Epacadostat

Stable Baseline INR	Epacadostat Dose		
	≤ 50-100 mg BID	200 mg BID	300 mg BID
INR ≤ 2.5	Close INR monitoring	Close INR monitoring	Reduce warfarin by ~33% and monitor INR
INR > 2.5	Close INR monitoring	Reduce warfarin by 20%-25% and monitor INR	Reduce warfarin by ~33% and monitor INR

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

8. TREATMENT DURATION

Patients will complete therapy unless one of the following criteria applies:

- Confirmed Disease progression per irRECIST
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse events or DLT
- Patient withdrawal from study (patient choice)
- Pregnancy
- Delay in epacadostat treatment > 30 days due to toxicity
- Failure of patient to adhere to study requirements
- Physician Discretion

8.1 Duration of Follow Up

All patients will be followed for 30 days after the last dose of treatment with the agent under this IND or until all treatment related clinical significant toxicities resolve to baseline or grade ≤ 1. Adverse events with attribution of possible, probable or definite will be reported following guidelines for adverse event reporting and all SAEs will be reported for 30 days after the last dose. Patients will be followed every 3 months per standard of care for PFS and OS.

8.2 Discontinuation Due to Disease Progression

Immunotherapeutic agents such as epacadostat and SD-101 may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents and can manifest as a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

Immune related RECIST will be used for assessment of tumor response for the purposes of managing subjects on Protocol treatment and decision making for discontinuation of study therapy due to disease progression. PD should be confirmed no earlier than 4 weeks later according to the criteria outlined in Table 8. Subjects who are deemed clinically unstable or who have biopsy proven new metastatic lesions are not required to have repeat imaging for confirmation. This decision will be based on clinical judgment of a subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. At a minimum, subjects must meet the following criteria for continued treatment on study after disease progression is identified at a tumor assessment:

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

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

- No decline in ECOG performance status.
- Absence of new or worsening symptoms.
- Absence of rapid progression of disease.
- Absence of progressive tumor at critical anatomical sites (e.g., spinal cord compression) requiring urgent alternative medical intervention.

Table 8: Imaging and Treatment after First Radiologic Evidence of Progressive Disease

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD	Repeat imaging at ≥ 4 weeks to confirm PD	May continue study treatment at the investigator's discretion while awaiting confirmatory scan	Repeat imaging at ≥ 4 weeks to confirm PD if possible	Discontinue treatment
Repeat scan confirms PD	No additional imaging required	Discontinue treatment	No additional imaging required	N/A
Repeat scan shows SD, PR, or CR[a]	Continue regularly scheduled imaging assessments every 6 weeks from Week 12 to Week 48 then every 12 weeks thereafter.	Continue study treatment at the investigator's discretion	Continue regularly scheduled imaging assessments every 6 weeks from Week 12 to Week 48 then every 12 weeks thereafter.	May restart study treatment if condition has improved and/or clinically stable per investigator's discretion

[a] SD, PR, CR is based on new baseline from first evidence of PD.

9. STUDY ASSESSMENTS AND MONITORING

The study calendar lists all the study assessments and their scheduled times. All data obtained from these assessments will be recorded in the study specific case report forms that will be generated prior to study activation. See Appendix 2 for study registration guidelines and Appendix 3 for data submission schedule.

9.1 Study Calendar

Assessment Window (Days)	Screening Days -28 to -1	Days 1, 8, 15, 22, 29 (±7days)	q 60 Day Visits[k] (±7days)	Follow-up[l]
Signed Informed Consent Form(s)	X			
Review of eligibility criteria	X			
Medical History	X			
Concomitant medications	X		X	X
Physical examination [a]	X	X	X	X
ECOG performance status	X	X	X	X
Vital signs	X	X	X	X
Weight	X	X	X	X
Height	X			
Hematology [b]	X	X	X	X
Serum chemistry [b]	X	X	X	X
Coagulation panel (aPTT/INR)	X			
EBV, HIV, HBV, HCV serology	X			
C-reactive protein testing	X			
TSH, free T3, free T4	X			
Serum pregnancy test if applicable	X			
Adverse events[c]		X	X	
Efficacy [d]			X	X
Investigational Treatment				
Epacadostat [e]		2x daily administration		
Intralesional SD-101[f]		X		
Radiation Therapy [g]		1st week		
Tumor Response Assessment				
CT or MRI [h]	X		X	X
Correlatives				
Blood samples for immune assays		X[i]	X[i]	
Biopsy		X[j]		
Stool Sample		X[m]		

Abbreviations: ECOG=Eastern Cooperative Oncology Group; EBV=Epstein Barr Virus; HIV=Human Immunodeficiency Virus; HBV=Hepatitis B Virus; HCV=Hepatitis C Virus; TSH=Thyroid Stimulating Hormone; T3=Triiodothyronine; T4=Thyroxine; DLT=dose limiting toxicity; FFPE=formalin-fixed, paraffin-embedded; CT=computerized tomography; RT=radiation therapy.

[a] Patients will be monitored once during the first week of radiotherapy, and with each intralesional SD-101 injection. Patients will be monitored every 30 days (+/- 7 days) thereafter for safety.

[b] Hematology and serum chemistry assessments should be obtained within 14 days of the first study treatment and don't need to be repeated on day 1. A complete blood count with differential and a comprehensive metabolic profile should be obtained for these studies. During follow-up these tests will be done every thirty days.

[c] Refer to Section 13.5 for procedures for reporting SAEs.

[d] ORR, DCR, and PFS will be assessed every 60 days using RECIST 1.1 and irRECIST.

[e] Epacadostat: 50-300 mg PO BID throughout the study period until progression.

[f] Intralesional SD-101: 4 mg injection into RT treatment lesion. 5 intralesional injections will be administered over a 5 week period on days 1, 8, 15, 22, and 29. The final two injections (on day 22 and 29) are optional for patients with visceral treatment lesions.

[g] Radiation therapy: Cohort 1 (solid tumors): 8 Gy × 3) or 4 Gy × 5); Cohort 2 (lymphoma): 8 Gy × 3, 4 Gy × 5, or 2 Gy × 2. All treatments must commence on day 1 after intralesional injection of SD-101. Fractions may be delivered on consecutive or every other day (a minimum of 12 hours and a maximum of 96 hours between treatments), but must be completed during week 1.

[h] CT or MRI at pre-treatment and every 60 days throughout the study period.

[i] Correlatives: Blood samples for immune assays will be collected on Day 1 and Day 15 and at 60 day clinical visits. See the correlative studies section for detailed information (Section 11.0).

[j] Biopsy: On Day 1 and Day 15 tumor biopsy will precede intralesional injection, RT, and epacadostat. See the correlative studies section for detailed information (Section 11.0). NOTE: The Day 1 biopsy and labs must be completed before starting protocol treatment.

[k] q 60 Day Visits: Patients will be followed with a imaging, labs, and clinic visit every 60 days during the first year of study. Brief visits for safety monitoring will occur every 30 days (+/- 7 days).

[l] Follow-up: All patients will be followed for 30 days after the last dose of treatment with the agent under this IND or until all clinical significant toxicities resolve to baseline or grade ≤ 1. Additional follow-up data will be gathered every 3 months from standard of care follow up visits and assessments after trial discontinuation.

[m] Stool sample will be collected from patients before initiation of treatment.

10. ASSESSMENTS TYPES

10.1 Efficacy

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [56] as well as irRECIST criteria. Additionally, imaging will be reviewed by a radiologist in conjunction with a radiation oncologist to help distinguish tumor progression from post-radiotherapy scarring. 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.

Disease Parameters

Measurable Disease
The presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Measurable Lesions
Lesions that can be accurately measured in at least one dimension with longest diameter 20mm using conventional techniques or 10mm with spiral CT scan.

Non-Measurable Lesions
All other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonitis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques**.**

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, preferably within two weeks of treatment initiation, 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.

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Methods of Measurements

CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

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

When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.

Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Response Criteria

Evaluation of Target Lesions

- **Complete Response (CR):** Disappearance of the target lesion
- **Partial Response (PR):** At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
- **Progressive Disease (PD):** At least a 20% increase in the sum of the LD of target lesion, or the appearance of one or more new lesions
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Evaluation of Best Overall Response

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

Table 9: Best Overall Response Evaluation

Best Overall Response Evaluation		
Target Lesion	**New Lesion**	**Overall Response**
CR	No	CR
PR	No	PR
SD	No	SD
PD	Yes or No	PD

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

In some circumstances it may be difficult to distinguish residual disease from normal tissue.

When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

Immune Related Response Criteria

A growing body of literature indicates that radiographic responses to immunotherapy may have different patterns and kinetics than what would be expected with traditional cytotoxic therapies. To account for these differences we will also characterize radiographic outcomes using the immune related response criteria outlined by Wolchok and colleagues [57]. See Appendix 6. This criteria will be used to measure the abscopal response rate and DCR (CR+PR+SD) and determine whether the study should proceed to stage 2 and is worthy of further study during the Simon two-stage study.

Confirmation

The main goal of confirmation of objective response is to avoid overestimating the response rate observed. For reporting the study outcomes the response rate and confirmed response rate will be made clear. For interval evaluation of response rates during the Simon-two stage study responses do not need to be confirmed for the study to progress. To be assigned the status of confirmed responses must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol. For PD all results should be confirmed as described in section 8.2.

Duration of Overall Response

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

Duration of Stable Disease

SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.

The clinical relevance of the duration of SD varies for different tumor types and grades, but in general, if two consecutive CT/MRI scans show stable disease, or the patient experiences four months of stable disease, then we will consider this to be stable disease

Therefore, it is highly recommended that the protocol specify the minimal time interval required between two measurements for determination of SD. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study.

Treatment Tolerability

Treatment tolerability will be measured as the percentage of patients who remain free of treatment intolerability as defined in section 6.6.

Abscopal Response Rate (ARR)

ARR is defined as the percentage of patients that achieve an objective tumor response at unirradiated lesions as defined by irRECIST criteria

Objective Response Rate

ORR is defined as the percentage of patients that achieve PR or CR.

Disease Control Rate (DCR)

DCR is defined as the percentage of patients that achieve an objective tumor response or have stable disease to therapy as best response and is defined as complete response (CR) + partial response (PR) + stable disease (SD). This endpoint has been shown to be more meaningful, and translating to survival advantage, in a number of tumor immunotherapy studies.

Progression-Free Survival (PFS)

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

Overall Survival (OS)

OS is defined as the duration of time from the start of treatment to death from any cause.

Reporting of Results

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 8) unknown (not assessable, insufficient data).

All of the patients who met the eligibility criteria should be included in the main analysis of the response rate. Patients in response categories 4-8 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration, or failure to complete all prescribed study therapy, does not result in exclusion from the analysis of the response rate. Sub-analyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). The reasons for excluding patients from the analysis should be clearly reported. There will be a planned analysis of patients who are evaluable for response (see section 12.4) which will be used for the Simon two-stage design.

The 95% confidence intervals should be provided.

10.2 Safety

Safety assessments will consist of monitoring and recording all adverse events, including serious adverse events, the monitoring of hematology, blood chemistry, coagulation parameters, urinalysis and the regular monitoring of vital signs, and physical condition as shown in corresponding tables. For details on AE collection and reporting, refer to the Safety section in the protocol.

10.3 All Study Variables

The panel of study endpoints and how they will be measured are described in Table 10.

Table 10: Study Variables

Endpoint	Variable	Measurement	Comment
Primary- Phase 1	MTD	CTCAE V4.03	Outlined in section 3. The maximum dose at which <2 of 6 patients experienced a DLT
Primary- Phase 1	DLT	CTCAE V4.03	Outlined in section 3. A DLT is defined as ≥ grade 4 injection site reacton OR ≥ grade 3 treatment-related non-hematologic toxicity (excluding injection site reactions) OR ORAST/ALT > 3 x ULN with bilirubin > 2 X ULN, OR pneumonitis that requires holding treatment > 14 days. Grade 3 rash will not be included as a DLT if there is no desquamation, no mucosal involvement, if it resolves without systemic corticosteroids by the next scheduled dose of epacadostat or 14 days, whichever is longer, and epacadostat dose intensity is maintained at 75% of planned dose during DLT period (i.e < 8 days of dose interruption). If epacadostat dose intensity cannot be maintained at 75% of planned dose during DLT period as a result of toxicity of any grade this will also be deemed a dose limiting toxicity.
Primary- Phase 2	Safety	CTCAE V4.03	
Primary-Phase 2	DCR (CR+PR+SD)	irRECIST	DCR is the endpoint for the Simon two-stage phase 2 study
Secondary- Phase 2	ARR	irRECIST	Objective response at unirradiated sites, the endpoint for measuring responses
Secondary- Phase 2	Treatment tolerability	CTCAE V4.03	Outlined in section 6.6. DLTs and any other treatment related adverse event requiring discontinuation of ERS therapy will be deemed treatment intolerability. Patients unable to resume epacadostat after 30 days due to toxicity will be labelled as having treatment intolerability. If more than two consecutives doses of SD-101 are missed due to toxicity the patient will be labeled as having treatment intolerability. Patients unable to receive at least 50% of the prescribed radiotherapy dose due to treatment

			toxicity will be labeled as having treatment intolerability.
Correlative	ORR	RECIST and irRECIST	
Correlative	PFS	RECIST and irRECIST	
Correlative	OS	RECIST and irRECIST	
Correlative	PBMC Immunophenotype	FACS	Blood
Correlative	PBMC gene expression	qPCR / Nanostring	Blood
Correlative	Systemic Cytokine Signature	Luminex	Serum
Correlative	Try/Kyn ratio	Mass spectrometry	Serum
Correlative	Tissue Immune Markers	IHC / IF	Tissue
Correlative	Tumor gene expression	qPCR / Nanostring	Tissue
Correlative	Mutational load	Whole exome sequencing/ RNA sequencing	Blood and Tissue
Correlative	T cell receptor diversity	TCR deep sequencing	Blood and Tissue
Correlative	Stool Microbiome	16s rRNA	Stool

11. CORRELATIVE SCIENCE

11.1 Rationale

One of the major shortcomings of immunotherapy trials has been the lack of in depth correlative studies to help identify the mechanism of action of these therapies, identify biomarkers of response, and provide a foundation for further improving these approaches. To address this we plan to perform in depth immunological analysis of patient blood and tumor samples. Pre- and post-treatment blood and tumor biopsies (when available) will be obtained as outlined in the study calendar. Briefly, blood and tumor samples will be collected pre-treatment on Day 1 and again at Day 15. Blood samples will also be collected at 60 day check-up visits. Optional blood and tumor biopsies can be obtained at progression. Participation in the correlative studies is mandatory unless waived by the study principal investigator due to safety concerns or other reasons. Archival tumor blocks will also be collected when available. We will evaluate immunologic changes systemically and in the tumor and tumor microenvironment within patient's pre to post therapy and across the cohort of patients to identify predictive biomarkers and elucidate the mechanistic immunologic effects of therapy. For further details, refer to Appendix 4 and Table 10 in Section 10.3. Correlative studies will include (in order of priority):

Blood

- FACS for quantification, immunophenotyping, and functional assessment of PBMCs

- qPCR (quantitative polymerase chain reaction) evaluation of immune gene signatures including: cytokines, T-cell activation markers, immunosuppressive enzymes and molecules (IDO [indoleamine-pyrrole 2,3-dioxygenase], arginase, CTLA-4, PD-1/PD-L1), macrophage polarization, etc.
- Nanostring gene panel
- Whole exome sequencing
- Evaluation of systemic plasma tryptophan to kynurenine ratios
- Luminex evaluation of plasma for systemic cytokine / chemokine signatures
- T-cell receptor (TCR) deep sequencing to determine clonal expansion of T-cells in the systemic circulation
- Other studies as deemed feasible and informative by the principal investigators

Tissue

- IHC to determine expression of markers including PD-1, PD-L1, CD8, CD4, IDO and FOXP3
- qPCR evaluation of the tumor microenvironment gene signatures including: cytokines, T-cell activation markers, immunosuppressive enzymes and molecules (IDO, arginase, CTLA4, PD-1/PD-L1), macrophage polarization, etc.
- Nanostring gene panel on FFPE tissues or snap frozen tissues
- Whole exome sequencing
- Other studies as deemed feasible and informative by the principal investigators

Stool

- Stool microbiome analysis

A comprehensive analysis of tumor, blood, and stool samples will provide valuable insight into potential biomarkers and into the mechanism of action of our combined therapy.

11.2 Correlative Study Design and Methodology

We have extensive expertise in all of the techniques described at the UC Davis Laboratory of Tumor Immunology. Blood samples will be separated into PBMCs and plasma and stored at -80 for batched analysis. PBMCs will be stained for FACS analysis using well characterized antibodies against markers such as CD45, CD3, CD4, CD8, FOXP3, Granzyme B, Interferon gamma, tumor necrosis factor (TNF) alpha, PD-1, etc. Results will be analyzed using a BD Fortessa multi-color flow cytometer and Flowjo software. An aliquot of PBMCs will also be set aside for RNA isolation and batched analysis of gene expression. mRNA (messenger ribonucleic acid) will be extracted using RNeasy kits (Qiagen) and reverse transcribed to cDNA. Cellular RNA will be analyzed by qRT-PCR (real-time reverse transcription-polymerase chain reaction) using verified primers to investigate the expression of genes

including IDO, arginase, iNOS (inducible Nitric oxide synthases), CTLA-4, PD-1, PD-L1 and others. RNA will also be analyzed using a Nanostring gene panel. To determine if certain clones of T cells are preferentially expanding after therapy, an aliquot of PBMCs will also be used for TCR deep sequencing. Plasma will be evaluated for systemic cytokine and chemokine signatures using Luminex technology. Markers will include IL-2, IL-6, IL-10, IL-12p70, GM-CSF (granulocyte-macrophage colony-stimulating factor), TNF alpha, IFN (interferon) gamma, CXCL10 (C-X-C motif chemokine 10), RANTES (regulated on activation, normal T cell expressed and secreted), MIP1 (Macrophage Inflammatory Protein) alpha, MIP1 beta, TGF-beta and others. Tissue biopsies will be formalin fixed and paraffin embedded using standard protocols. Tissue will be analyzed by IHC staining for PD-1, PD-L1, FOXP3, CD8, and CD4 markers. If sufficient biopsy material is available then a tissue sample will be stored in RNA later for batched analysis by qPCR / Nanostring as described above. Whole exome sequencing will also be performed on tumor tissue and compared to the peripheral blood as a normal tissue control to determine the mutational load of the tumor. Pre-treatment stool samples will be collected to analyze the gut microbiome.

12. DATA AND STATISTICAL ANALYSIS PLAN

12.1 Sample Size

For the dose escalation phase a traditional 3 + 3 design will be used with the goal of determining the MTD through DLT assessment. Per design each cohort will consist of 3-6 patients. The number of patients will depend on the occurrence of DLT (Table 1). We estimate a minimum of 6 patients and a maximum of 18 patients (6 patients/cohort) would be enrolled. Once the MTD is determined patients will be enrolled into either a lymphoma or a solid tumor phase 2 cohort which will generate preliminary efficacy data to determine if the treatment regimen should be considered for a randomized study. Patients treated at the MTD during the phase I will also be used as part of the phase II cohorts to minimize patient numbers. For the solid tumor cohort (cohort 1) we have set a threshold DCR response rate of 20% by irRECIST as worthy of further study and this cohort will enroll 16-30 evaluable patients. In the first stage 16 patients (n1) will be enrolled and greater than 1 response (r1) is required for the trial to proceed. In the second stage an additional 14 patients will be enrolled for a total of 30 patients (nTot) and greater than 3 responses (rTot) are required for the therapy to be deemed worthy of further study in a randomized trial. For the lymphoma cohort (cohort 2) we have set a threshold DCR response rate of 30% by irRECIST as worthy of further study and this cohort will enroll 7-14 evaluable patients. In the first stage 7 patients (n1) will be enrolled and greater than 0 responses (r1) are required for the trial to proceed. In the second stage an additional 7 patients will be enrolled for a total of 14 patients (nTot) and greater than 2 responses (rTot) are required for the therapy to be deemed worthy of further study in a randomized trial. Patients who are not evaluable for treatment efficacy (see section 12.4) will

not be included in the simon two-stage analysis and will be replaced by additional patient enrollment to ensure a full cohort of evaluable patients.

The primary endpoint of this study is to determine the MTD of epacadostat when combined with SD-101 and radiotherapy. In the two phase II expansion cohorts we will further assess safety and efficacy of this regimen at the proposed MTD. The expansion will employ a Simon two-stage design to determine if the treatment efficacy warrants further investigation in a randomized study. The sample size was determined by the dose-escalation design combined with a Simon two-stage design for our required efficacy endpoints. When the true response rates are at their respective thresholds both two-stage designs have 80% to reject at the 0.05 level (1-sided) the null hypothesis that the DCR response rate is an unacceptably low 5%. Since patients treated at the MTD will be included in the phase II expansion analysis a maximum of 56 evaluable patients will be enrolled.

12.2 Statistical Analysis Plan

Descriptive statistics will be used. All data will be summarized by dose cohort, dose expansion and overall subject population. A planned subset analysis on patients who have or have not received previous immunotherapy will be performed. A planned subset analysis based on histologic tumor type will be performed.

12.3 Safety

The adverse events observed will be summarized as frequency, proportion of patients, and exact 95% confidence interval for proportion, categorized by type (organ affected or laboratory determination), severity by CTCAE v4.03 and nadir or maximum values for the laboratory measures), time of onset (i.e. course number), duration, and reversibility or outcome. Tables will be created to summarize these toxicities by dose and course.

12.4 Efficacy

As a secondary endpoint, all responses will be reported using irRECIST and RECIST 1.1 definitions [56]. Because of the potential heterogeneity of the patients, all results will be considered preliminary and hypothesis generating for future studies. Response rate will be summarized by exact binomial confidence intervals. Disease free survival will be summarized with Kaplan-Meier plots to describe the outcome of patients treated on this protocol. The median DFS time will be estimated using standard life table methods.

If a patient is enrolled on the study and is subsequently removed from treatment for any reason prior to the first CT/MRI scan they are not evaluable for treatment efficacy, that patient will not be included in analysis of treatment efficacy specific to response criteria, but will still be included in the general safety analysis with all other patients. Patients who are not evaluable for treatment efficacy will be replaced by additional patient enrollment to ensure a full cohort of evaluable patients.

12.5 Subject Course

Information regarding the subject's course such as completing the study treatment, dose delays, premature discontinuation and major protocol violation will be tabulated and summarized.

12.6 Correlative Laboratory Markers

Correlative biomarker endpoints are exploratory and hypothesis generating. Descriptive statistics will be applied to characterize differences within a given patient pre-treatment to post-treatment and across the cohorts of patients. Changes in the correlative endpoints will be evaluated using a two-tailed paired Student's t-test. To provide a preliminary estimate of the predictive or prognostic value of the various correlative endpoints for DFS we will be using multiple regression analysis with ordinal category for response (generalized linear models) or time to event (proportional hazards regression) as the outcome.

13. SAFETY REPORTING OF ADVERSE EVENTS

13.1 Assessment of Safety

Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) that are considered related to THERAPY, all events of death, and any study specific issue of concern.

13.2 Risks Associated With

Although most immune-related AEs observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications.

13.3 Adverse Events

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with disease that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations).

- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

13.3.1 Serious Adverse Events

An AE should be classified as an SAE if the following criteria are met:

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

13.4 Methods and Timing for Assessing and Recording Safety Variables

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study are collected and reported to the FDA, appropriate IRB(s), Incyte, Inc. and, Dynavax, Inc. in accordance with CFR 312.32 (IND Safety Reports).

13.4.1 Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins at initiation of study treatment and ends 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

13.4.2 Assessment of Adverse Events

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start

and end dates), regulatory seriousness criteria if applicable, suspected relationship to the therapy and radiotherapy (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Yes (Possibly, Probably, or Definitely)

There is a plausible temporal relationship between the onset of the AE and administration of the therapy, and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the therapy; and/or the AE abates or resolves upon discontinuation of the therapy or dose reduction and, if applicable, reappears upon re-challenge.

No (Unlikely, Unrelated)

Evidence exists that the AE has an etiology other than the therapy (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to therapy administration (e.g., cancer diagnosed 2 days after first dose of study drug).

Expected adverse events are those adverse events that are listed or characterized in the Package Insert or current Investigator Brochure.

Unexpected adverse events are those not listed in the Package Insert (P.I.) or current Investigator Brochure (I.B.) or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

13.5 Procedures for SAE Reporting

13.5.1 Initial Reports

1. The Investigator reports to Incyte every SAE, regardless of suspected causality, which occurs after the subject has signed informed consent and up to the time that subject has completed the trial, including any post-treatment follow-up required by the protocol. Such cases are regarded as originating in the IST for the purpose of notification to Incyte.
2. The investigational site notifies Incyte of an SAE ***within 24 hours*** of the Investigator becoming aware of the SAE, regardless of causality to the investigational product.

   The investigational site records all SAE details on the Serious Adverse Event Report Form, or on the SAE form being used by the Investigator conducting the trial, and e-mails the report to Incyte via the address: IncytePhVOpsIST@incyte.com.

The investigational site does ***not*** provide medical records (e.g., discharge summary, relevant test results) unless requested by Incyte. Instead, the investigational site records the information relevant to the SAE on the SAE form and provides the form to Incyte.

If a non-serious AE becomes serious, the investigational site follows the process for SAE reporting.

The Incyte PhV representative, in conjunction with the Incyte PhV Service Provider, reviews the initial SAE information and determines whether the criteria for a valid case (patient ID, enrolment number, randomization number, age, sex, event, reporter name, site number, and suspect drug) are present, and assesses the report for completeness.

If necessary, the Incyte PhV representative or designee queries the investigational site (within 48 hours of receipt) for additional information to ensure a valid case prior to distributing the report for internal Incyte review.

The internal Incyte review occurs as specified in the internal Incyte SAE distribution list for IST protocols.

The report should not be delayed pending an Investigator causality assessment.

3. The Incyte PhV representative, in conjunction with the Incyte review team, ensures that all information available at the time, which is relevant to the medical/safety evaluation of the report, is collected and included without compromising the timeframes for regulatory reporting.

   If only partial information is available, the report will not be delayed and must be reported to satisfy the reporting timeframe. Any additional information should be collected for a follow-up report to Health Authorities (HAs).

13.5.2 Follow-up Reports

1. When new information regarding the SAE, or outcome of pregnancy, becomes available, the investigational site personnel update all relevant data on the appropriate SAE Report Form, or equivalent, with any new or changed information and send the follow-up SAE report to Incyte ***within 24 hours*** of becoming aware of the new information, via e-mail to IncytePhVOpsIST@incyte.com.

   This includes any SAE that is upgraded to fatal or life-threatening.

2. Incyte's PhV Service Provider tracks any critical outstanding follow-up information and questions, and contacts the investigational site via a faxed Data Clarification Form (DCF) to request the information until all outstanding queries are resolved.

   This may include requests for hospital discharge summaries, autopsy reports, death certificates (if applicable), and/or results of relevant laboratory and diagnostic tests.

   After three attempts to resolve queries, which are sent at two-week intervals, the PhV Service Provider notifies the Incyte PhV representative of any outstanding queries. The Incyte PhV representative notifies the Incyte IST PM of the outstanding queries that require follow-up.

   Incyte PhV will discuss with the Incyte IST PM action plans for non-responsive sites (e.g., certified letter, site visit), as needed.

3. The investigational site faxes the DCF response to the PhV Service Provider, using the fax number provided on the Fax transmission sheet from the PhV Service Provider.
4. The PhV Service Provider appends to the case, in the safety database, all additional documentation submitted by the site and generated during follow-up SAE collection, including the Incyte internal SAE questions and/or copies of the amended SAE reports.

13.6 Regulatory Reporting

If an event is serious, unexpected, and suspected to be related to the investigational product, the event is considered to be reportable to Health Authorities (HAs) as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

An event is determined to be unexpected if it is not listed in the current Reference Safety Information (e.g., Investigator's Brochure (IB)) or when the specificity or severity of the event is not consistent with the current Reference Safety Information.

Fatal or life-threatening SUSARs must be reported to the required HA(s) within 7 calendar days after the Sponsor's initial receipt of information.

All other SUSARs must be reported to the required HA(s) within 15 calendar days after Sponsor's initial receipt of information.

The Sponsor-Investigator reports all SUSARs to the FDA under the Investigator's IND.

Incyte is responsible for the following:

- Meeting expedited reporting requirements to HAs in their respective territories

- Cross-reporting any SUSAR originating from the IST to the applicable Incyte IND(s)
- Distributing Investigator Notifications to Investigators participating in the applicable Incyte IND(s)

13.7 Procedure for Reporting Pregnancy

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

Within 72 hours of learning of the pregnancy, the investigational site completes the Clinical Trial Pregnancy Form (sections I, II, and question 18 in section III) or equivalent, and e-mails the report to Incyte at IncytePhVOpsIST@incyte.com.

Within 72 hours of learning of the abnormal outcome of the pregnancy (for example, delivery, termination, or miscarriage, abnormal newborn), the investigational site completes the Clinical Trial Pregnancy Form (sections II, III, IV, and V) or equivalent, and e-mails the report to Incyte at IncytePhVOpsIST@incyte.com. Delivery of normal new born will be reported to Incyte in 7 days of learning.

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

Any SAE occurring during pregnancy must be reported to Incyte as an SAE, in accordance with Section 3 of this Plan.

13.8 Additional Reporting Requirements for IND Holders

For Investigator-Sponsored IND Studies, some additional reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR § 312.32. Events meeting the following criteria need to be submitted to the Food and Drug Administration (FDA) as expedited IND Safety Reports according to the following guidance and timelines:

7 Calendar Day Telephone or Fax Report:

The Investigator is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the use of therapy. An unexpected adverse event is one that is not already described in the therapy Investigator Brochure. Such reports are to be telephoned or faxed to the FDA and Incyte within 7 calendar days of first learning of the event.

15 Calendar Day Written Report

The Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered reasonably or possibly related to the use of THERAPY. An unexpected adverse event is one that is not already described in the THERAPY investigator brochure.

Written IND Safety reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed by the investigator with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, Incyte, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500 form, but alternative formats are acceptable (e.g., summary letter).

Under requirements of 21 CFR312.23, the completed MedWatch form and FDA Form 1571 must be sent to the FDA..

FDA fax number for IND Safety Reports:

1 (800) FDA 0178

All written IND Safety Reports submitted to the FDA by the Investigator must also be faxed to UC Davis IRB per institutional policies:

IRB Administration
2921 Stockton Blvd
Suite 1400, Room 1429
Sacramento, CA 95817
Phone: (916) 703-9151
Fax: (916) 703-9160

13.9 Study Close-Out

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Incyte. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Incyte.

14. ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

14.1 Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and Good Clinical Practice, as described in:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.
2. Directive 91/507/EEC, The Rules Governing Medicinal Products in the European Community.
3. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
4. Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996).

The investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

14.2 Institutional Review Board/Independent Ethics Committee

Before implementing this study, the protocol, the proposed informed consent form and other information to subjects, must be reviewed by a properly constituted Institutional Review Board/Independent Ethics Committee (IRB/IEC/REB). A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to Incyte before study initiation. The name and occupation of the chairman and the members of the IRB/IEC/REB must be supplied to Incyte. Any amendments to the protocol, other than administrative ones, must be approved by this committee.

14.3 Study Documentation

The required documents include, but are not limited to the following: IRB approvals (i.e., protocol, consent form, amendments, patient brochures and recruitment material, etc.), IRB membership rosters, summary of unanticipated problems or protocol deviations, and documentation of expertise of the investigators.

14.4 Informed Consent

The investigator must explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time

and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the subject cannot read or sign the documents, oral presentation may be made or signature given by the subject's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the patient could not read or sign the documents. No patient can enter the study before his/her informed consent has been obtained.

The informed consent form is considered to be part of the protocol, and must be submitted by the investigator with it for IRB/IEC/REB approval.

Fertile men and women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study.

Acceptable methods of birth control for men and women are the following:

Highly effective methods

- Male sterilization (vasectomy). For female patients, the vasectomized male partner should be the only partner
- True abstinence, if this is your preferred and usual lifestyle
- Hormonal birth control for male patient's partner

Effective methods

- Placement of intrauterine device or intrauterine system
- Condom with spermicidal foam/gel/film/cream/suppository
- Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository

Unacceptable methods

- Abstinence at certain times of the cycle only, such as during the days of ovulation, after ovulation (based on symptoms or temperature)
- Pre-ejaculatory withdrawal

If there is any question that the patient will not reliably comply, they should not be entered in the study.

In accordance with UCD OCR policy an original signed and dated participant Informed Consent document will reside in a secured location at participating institutions. Copies of the signed and dated Informed Consent document will be provided to the study participant and a copy will be stored in the patient's electronic medical record at the participating institution.

14.5 Discontinuation of Study Support

Incyte reserves the right to discontinue support for any study under the conditions specified in the clinical trial agreement.

14.6 Amendments to the Protocol

Any change or addition to this protocol requires a written protocol amendment that must be approved by Incyte and the investigator before implementation. Any protocol amendment requires approval by the IRB/IEC/REB. A copy of the written approval of the IRB/IEC/REB, must be sent to Incyte.

14.7 Patient Confidentiality

In order to maintain patient privacy, all study reports and communications will identify the patient by initials and the assigned patient number. Data capture records and drug accountability records will be stored in secure cabinets in the department of radiation oncology, UC Davis or at the participating institutions. Medical records of patients will be maintained in strict confidence according to legal requirements. The investigator will grant monitor(s) and auditor(s) from Incyte or its designees and regulatory authority(ies) access to the patient's original medical records for verification of data gathered on the data capture records and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

14.8 Protocol Deviations

All protocol deviations will be reported in accordance with UCD IRB Administration and UCD Cancer Center OCR policies.

14.9 Quality Assurance

Quality assurance audits of select patients and source documents may be conducted by the Quality Assurance and/or Data Safety Committees at participating institutions or UC Davis Cancer Center as outlined in the UC Davis Cancer Center Data and Safety Monitoring plan.

15. OVERSIGHT AND MONITOROING

15.1 Data and Safety Monitoring

In addition to the requirements for adverse event reporting as outlined in Section 7.0, this protocol is also subject to the UC Davis Cancer Center's (UCDCC) Data and Safety Monitoring Plan. The UCDCC is committed to pursuing high-quality patient-oriented clinical research and has established mechanisms to ensure both scientific rigor and patient safety in the conduct of clinical research studies. The UCDCC relies on a multi-tiered committee system that reviews and monitors all cancer clinical trials and ensures the safety of its participants, in compliance with institutional and federal requirements on adverse event (AE) reporting, verification of data accuracy, and adherence to protocol eligibility requirements, treatment guidelines, and related matters. The Scientific Review Committee (SRC) assumes overall oversight of cancer studies, with assistance and input from two independent, but interacting, committees: the Quality Assurance Committee and the Data and Safety Monitoring Committee. A multi-level review system strengthens the ability of the UCDCC to fulfill its mission in conducting high quality clinical cancer research.

The principal investigator (PI) and clinical research coordinator will meet at least monthly for ongoing study information, to discuss patient data and adverse events and to determine if dose escalation is warranted, when applicable.

According to the UCDCC Data and Safety Monitoring Plan, any new serious adverse events related to the drugs being used on this trial are reviewed monthly by the UCDCC Data and Safety Monitoring Committee and any applicable changes to the study are recommended to the PI, if necessary.

The UCDCC SRC determines if a UCDCC Data and Safety Monitoring Board (DSMB) is required. If required, the Data and Safety Monitoring Committee will appoint a DSMB. The DSMB is responsible for reviewing study accrual logs, adverse event information and dose escalation meeting minutes (where applicable) to ensure subject safety and compliance with protocol defined guidelines.

The Research Monitor is responsible to oversee the safety of the research and report observations/findings to the IRB or a designated institutional official. The Research Monitor will review all unanticipated problems involving risks to subjects or others associated with the protocol and provide an independent report of the event to the IRB. The Research Monitor may discuss the research protocol with the investigators; shall have authority to stop a research protocol in progress, remove individual human subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report; and shall have the responsibility to promptly report their observations and findings to the IRB or other designated official and the HRPO.

15.2 Investigator Monitoring Guidelines

Investigators will conduct continuous review of patient safety. As mentioned in section 3.0, patients will be monitored weekly during the 30 day DLT period and every 30 days for the remaining of the study. All patients on active treatment will be discussed at weekly conferences that are held at the University of California Davis. Per Cancer Center guidelines, a trial cannot proceed to the next dose level until a DLT meeting is conducted to comprehensively review all toxicity data and approve the dose de-escalation. The discussion will include for each dose level: the number of patients, significant toxicities as described in the protocol, doses adjustments, and responses observed.

All patients will be monitored for a minimum of 12 months to evaluate for long-term radiation effects. Preliminary efficacy as determined by ARR, ORR, DCR and DFS will be assessed every 60 days during the study period.

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17. APPENDICES

17.1 Appendix 1: Performance Status Scale

Karnofsky Status	Karnofsky Grade**	ECOG Grade	ECOG Status**
Normal, no complaints	100	0	Fully active, able to carry on all pre-disease performance without restriction
Able to carry on normal activities. Minor signs or symptoms of disease	90	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
Normal activity with effort	80		
Care for self. Unable to carry on normal activity or to do active work	70	2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
Requires occasional assistance, but able to care for most of his needs	60		
Requires considerable assistance and frequent medical care	50	3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
Disabled. Requires special care and assistance	40		
Severely disabled. Hospitalization indicated though death nonimminent	30	4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
Very sick. Hospitalization necessary. Active supportive treatment necessary	20		
Moribund	10		
Dead	0	5	Dead

* KPS will be used in this study. ECOG status is listed for reference.

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17.2 Appendix 2: Study Registration

A. Registrations for this protocol must be made through the department of radiation oncology, University of California, Davis Cancer Center between normal business hours (Pacific Time), Monday through Friday (except holidays). Documentation of current IRB approval of this protocol by non-UCD institutions must be on file prior to registration of patients at these institutions.

B. Pre-study laboratory tests, scans, and x-rays, must be completed prior to registration, within the time frame specified in the protocol. The eligibility checklist must be completed. Patients must sign an informed consent prior to registration.

C. If the patient is to be registered the same day as the proposed treatment start date, the UC Davis Study Coordinator must be notified by fax ([redacted]) and/or email 24 hrs prior to proposed treatment start date that the site has a patient to register.

D. Patients may be registered up to 72 hrs prior to treatment initiation. The signed consent, completed checklist and reports from all pre-study laboratory tests, scans and x-rays must be faxed/email to the University of California, Davis Comprehensive Cancer Center Office of Clinical Research in order to register the patient. The UC Davis Study Coordinator will review these documents and fax a registration confirmation within 24 hours. **NOTE: Administration of study medication may not be initiated until the registration confirmation has been received.**

E. A patient failing to meet all protocol requirements may not be registered. If you have any questions regarding eligibility, please contact the PI or Study Coordinator

17.3 Appendix 3: Data Submission Schedule

All data will be collected using UC Davis data collection forms. Any and all source documentation should be maintained.

- SUBMIT WITHIN 24 HOURS OF REGISTRATION:
  Patient Registration Form
- SUBMIT WITHIN 14 DAYS OF REGISTRATION:
  In-House Pre-Study Evaluation Form (IH-102)
- SUBMIT WITHIN 7 DAYS OF SCREENING FAILURE:
  Patient Screen Failure Form
- SUBMIT WITH 14 DAYS OF CYCLE COMPLETION:
  Adverse Event/Drug Relationship Form
- SUBMIT WITHIN 14 DAYS OF END OF EACH TREATMENT CYCLE:
  In-House Treatment Cycle Form – Infusion
- SUBMIT WITHIN 14 DAYS OF EACH RESPONSE ASSESSMENT:
  Tumor Measurement Log
- SUBMIT WITHIN 14 DAYS OF OFF TREATMENT:
  Off Treatment/In Follow-up/Off Study/Expiration Form (IH-301)
- SUBMIT WITHIN 14 DAYS OF KNOWLEDGE OF DEATH IF PATIENT IS STILL ON STUDY OR 30–DAYS IF OFF STUDY:
  Off Treatment/In Follow-up/Off Study/Expiration Form (IH-301)
- SUBMIT WITHIN 2 DAYS OF KNOWLEDGE OF PROTOCOL DEVIATION:
  Clinical Trials Support Unit: Notice of Protocol Deviation
- SUBMIT WITHIN 14 DAYS OF EACH REQUIRED FOLLOW-UP ENCOUNTER:
  Follow-Up Form (IH-302)
- ALL SERIOUS ADVERSE EVENTS MUST BE REPORTED AS OUTLINED IN THE PROTOCOL.

17.4 Appendix 4: Molecular Correlative Sample Handling

Specimen Submission for Correlative Studies:
Participation in these molecular correlative studies is mandatory. With the patient's consent, tissue and blood specimens will be submitted as outlined below. Samples will be de-identified and coded with a new patient ID number to protect patient's identity.

A specimen submission form should be filled out for each specimen obtained. All specimens must be labeled with protocol number, site identification, patient registration number, date of specimen collection, and number of cells (for PBMCs) or weight of tissue (for tissue biopsies). Correlative studies will be performed at UC Davis or samples will be shipped in a de-identified manner to other institutions / companies for analysis.

For correlative studies the following samples should be collected:

1) Peripheral blood samples obtained pre-treatment on day 1, then again at day 16 and at the q60 day follow-up visits.
2) Fresh tumor biopsy pre-treatment on day 1 and at day 15. Optional biopsy at progression.
3) Stool sample collected pre-treatment.

Correlative studies will include (in order of priority):

Blood

1) Flow Cytometry quantification, immunophenotyping, and activation / functional assessment of tumor infiltrating immune cells including myeloid-derived suppressor cells (MDSC), regulatory T (Treg) cells, T/B/NK cell immunophenotyping and activated T cells
2) RNA extraction for qPCR and Nanostring analysis
3) Whole exome sequencing (WES) as a normal tissue control to identify putative neo-antigens
4) Evaluation of systemic plasma tryptophan to kynurenine ratios
5) Peripheral blood cytokine / chemokine profiling by Luminex
6) T-cell receptor (TCR) deep sequencing to determine clonal expansion of T-cells in the systemic circulation
7) Other studies as deemed feasible and informative by the principal investigators

Tissue

1) IHC to assess tumor infiltrating immune cells (CD8, CD4, FoxP3) and expression of other markers with potential prognostic and/or predictive value on efficacy outcomes including IDO, PD-1 and PD-L1 as well as new biomarkers.
2) RNA extraction for qPCR and Nanostring analysis

3) Identification of tumor neo-antigens by RNA deep sequencing in conjunction with peripheral blood WES data.
4) Other studies as deemed feasible and informative by the principal investigators

Stool
1) Stool microbiomes analysis by 16s RNA sequencing

1.0 Peripheral Blood

1.1 Blood Collection

Blood specimens (4 x 5ml lavender top EDTA tubes) will be collected from each patient prior to initiating treatment at day 1 then again at Day 15 and at q60 day follow up visits as indicated in the study calendar**.** It is important that each tube be filled to 5ml to ensure sufficient specimens for the planned analyses. If possible, a blood specimen should be obtained at the time the patient is removed from protocol treatment or if the patient's disease progresses.

2.2 Blood Specimen Processing and handling – lavender top EDTA tubes

Four 5ml lavender top EDTA tubes will be collected from each patient at each time point. Each purple-top (EDTA) tube should be inverted several times, placed on wet ice, and delivered to the lab immediately. Every effort should be made to process blood samples within 1 hour of collection. Samples should be processed in sterile fashion.

The tube should be centrifuged as soon as possible at approximately 1,000-1,500 rpm (400 x g) for 10 minutes. The Plasma layer should be removed and kept on ice (see 1.2.1). PBMCs should be separated using sterile and endotoxin free Ficoll density gradient solution. The peripheral blood mononuclear cells (PBMCs) should be removed and pooled. The PBMC layer should be resuspended in three times the volume of cold sterile PBS. Cells should be counted using a hemocytometer and the total cell number should be noted. The expected yield is 1-2 million cells per ml of blood.

The PBMCs collected from 4 lavender top tubes will be divided into three aliquots. Roughly half of the cells should be cryopreserved for future analysis. The second aliquot consisting of roughly 25% of the cells will be placed in RNAlater and snap frozen with liquid nitrogen and stored at -70 to -80°C for future RNA extraction. The third aliquot consisting of the last 25% of cells will be snap frozen in liquid nitrogen and stored at -70 to -80°C for future DNA extraction. If there are more than 20 x 10^6 viable cells the RNA and DNA extraction aliquots should be limited to a total of 5 x 10^6 cells each and the additional cells should be cryopreserved thus deviating from the 2:1:1 aliquoting.

1.2.1 Blood plasma

The removed plasma layers should be pooled and centrifuged at 1000 x g for 10 minutes to clarify the plasma. The plasma should then be placed in up to eight 0.5 ml aliquots in labeled cryotubes. Any additional plasma can be discarded. The plasma will be frozen (snap frozen with liquid nitrogen if possible) and stored at -70 to -80°C. Samples should be batched and shipped overnight on dry ice to UC Davis at the address indicated. One to two tubes of plasma per patient will be shipped to Transgene in a batched manner from UC Davis.

1.2.2 Cryopreservation

After counting, PBS washed PBMCs should be divided into aliquots of 5 million cells and spun down at approximately 1,000-1,500 rpm (400 x g) for 10 minutes. Each aliquot should be resuspended in 1ml of cold sterile CryoStor CS10 freeze media (catalog number 07930, STEMCELL technologies) which contains 10% DMSO. Each 1ml aliquot should be placed in a cryopreservation tube and the lid should be tightly secured. Tubes should be placed into a "Mr. Frosty" or other slow freeze container and placed into a -70 to -80°C freezer for 12-24 hours. Tubes should then be transferred to and stored in vapor phase liquid nitrogen (-135°C). In a batched manner tubes should be shipped overnight in liquid nitrogen to UC Davis at the indicated address.

1.2.3 RNA later

After counting, PBS washed PBMCs should be spun down at approximately 1,000-1,500 rpm (400 x g) for 10 minutes. The cell pellet should be re-suspended in 1ml of RNAlater solution snap frozen in liquid nitrogen and stored at -70 to -80°C. In a batched manner tubes should be shipped overnight on dry ice to UC Davis at the indicated address. Please note that PAXgene tubes will not be used for collection of PBMCs for RNA analysis.

1.2.4 Snap frozen for DNA extraction

This specimen will be collected from the pre-treatment blood draw only. After counting, PBS washed PBMCs should be spun down at approximately 1,000-1,500 rpm (400 x g) for 10 minutes. The cell pellet should be snap frozen in liquid nitrogen and stored at -70 to -80°C. In a batched manner tubes should be shipped overnight on dry ice to UC Davis at the indicated address.

1.3 Peripheral Blood Analysis

1.3.1 Plasma

Plasma samples will be stored at UC Davis for batched analysis. Plasma will be interrogated for chemokine and cytokine levels using the luminex platform. Additionally, plasma samples will be evaluated for tryptophan to kynurenine ratios.

1.3.2 Cryopreserved samples

Cryopreserved samples will be stored at UC Davis for batched analysis. Samples will be thawed and stained with fluorophore-conjugated antibodies against CD4, CD8, CD25, CD62L, CD45RA, CD127, ICOS, PD-1, PD-L1, FoxP3, CD3, CD56, CD16, CD83, TIM-3, Ki-67, CD19, CD20, CD33, CD15, CD11b, HLA-DR and others. Stained cells will be interrogated by flow cytometry and results analyzed using FlowJo software.

1.3.3 RNAlater samples

Cells in RNA later will be stored at UC Davis for batched analysis. Samples will be thawed and RNA will be extracted. The transcriptome will be analyzed using a nanostring 770 gene panel. Targeted RT-PCR will be used to validate genes of interest.

1.3.4 Snap frozen samples

Snap frozen cell pellets will be stored at UC Davis for batched analysis. Samples will be thawed and genomic DNA will be extracted. Whole exome sequencing will be performed using the Illumina HiSeq platform.

2.0 Fresh tumor biopsy

2.1 Tumor biopsy collection

Fresh tumor biopsy is collected pre-treatment and at day 15. Optional biopsy can be obtained at progression. Tumor biopsies should be collected by core needle biopsy using the largest bore needle and number of passes deemed safe. The same lesions should be targeted for all fresh tissue biopsies. Confirmation that the core biopsies contain tumor should be performed at the time of biopsy using touch prep.

2.2 Tumor biopsy processing and handling

On site at the time of the biopsy tumor tissues should be aliquoted into two portions. The top priority assay is IHC/IF and biopsy samples should be placed in formalin fixative and later embedded into FFPE blocks. In general samples should be placed in fixative at a 10:1 ratio and fixed for at least 48 hours but thicker tissue samples may require longer fixation.

If sufficient tissue is available (which there generally should be if more than one biopsy pass has been undertaken) then no less than 10mg and but preferably 20 - 50mg of tumor tissue should be placed in 1ml of RNAlater snap frozen in liquid nitrogen and stored at -70 to -80°C.

2.3 Tumor biopsy analysis

FFPE tissue biopsy blocks will be collected and stored at UC Davis. Tissues will be sectioned, prepared, and mounted for IHC/IF using standard procedures. When possible, IHC/IF should be performed within two weeks of slide sectioning. Biopsy samples will be stained by multi-plex IHC/IF at UC Davis or collaborating laboratories to immunologically profile the tumor microenvironment. Markers examined will include CD3, CD8, CD4, FoxP3, Ki-67, PD-1 and PD-L1.

Tissue in RNA later will be stored at UC Davis for batched analysis. Samples will be thawed and RNA will be extracted. The transcriptome will be analyzed using a nanostring 770 gene panel. Targeted RT-PCR will be used to validate genes of interest. RNAseq data will also be used in conjunction with PBMC WES to identify mutational load and putative neoantigens.

3.0 Stool Sample Collection

3.1 Stool sample collection

Stool samples will be collected by the patient pre-treatment using the provided stool collection kit. Stool samples will be stored on ice in the kit provided and returned to UC Davis preferably within 12 hours (an no longer than 24 hours) of collection.

3.2 Stool sample processing and handling

Stool samples will be snap frozen in liquid nitrogen and stored at -70 to -80°C for batched analysis.

3.3 Tumor biopsy analysis

16s RNA will be extracted and sequenced from stool samples to determine the microbiome profile.

17.5 Appendix 5: Anaphylaxis Precautions

EQUIPMENT NEEDED

- Tourniquet
- Oxygen
- Epinephrine for subcutaneous, intravenous, and/or endotracheal use in accordance
- with standard practice
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

1. In the event of a suspected anaphylactic reaction during drug administration, the following procedures should be performed:
2. Stop the study drug administration.
3. Apply a tourniquet proximal to the injection site to slow systemic absorption of drug. Do not obstruct arterial flow in the limb.
4. Maintain an adequate airway.
5. Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
6. Continue to observe the patient and document observations.

17.6 Appendix 6: Immune-Related Response Criteria

Increasing clinical experience indicates that traditional response criteria (e.g., Response Evaluation Criteria in Solid Tumors, Version 1.1 [RECIST v1.1] and World Health Organization [WHO]) may not be sufficient to characterize fully activity in the new era of target therapies and/or biologics. In studies with cytokines, cancer vaccines, and monoclonal antibodies, complete response, partial response, or stable disease has been shown to occur after an increase in tumor burden as characterized by progressive disease by traditional response criteria. Therefore, conventional response criteria may not adequately assess the activity of immunotherapeutic agents because progressive disease (by initial radiographic evaluation) does not necessarily reflect therapeutic failure. Long-term effect on the target disease must also be captured. The immune-related response criteria (irRC) are criteria that attempt to do that by enhancing characterization of new response patterns that have been observed with immunotherapeutic agents (i.e., ipilimumab) [57]. (Note: The irRC only index and measurable new lesions are taken into account.)

GLOSSARY

Term	Definition
SPD	Sum of the products of the two largest perpendicular diameters
Tumor burden	$SPD_{\text{index lesions}} + SPD_{\text{new, measurable lesions}}$
Nadir	minimally recorded tumor burden
irCR	immune-related complete response
irPD	immune-related progressive disease
irPR	immune-related partial response
irSD	immune-related stable disease
irBOR	immune-related best overall response

BASELINE ASSESSMENT USING irRC

Step 1. Identify the index lesions (five lesions per organ, up to ten visceral lesions and five cutaneous lesions).

Step 2. Calculate the SPD of all of these index lesions:

$SPD = \sum_{i}$ (Largest diameter of lesion i) × (Second largest diameter of lesion i).

POST-BASELINE ASSESSMENTS USING irRC

Step 1. Calculate the SPD of the index lesions.

Step 2. Identify new, measurable lesions (≥ 5 × 5 mm; up to five new lesions per organ: five new cutaneous lesions and ten visceral lesions).

Step 3. Calculate the SPD of the new, measurable lesions.

Step 4. Calculate the tumor burden:

Tumor burden = $SPD_{\text{index lesions}} + SPD_{\text{new, measurable lesions}}$

Step 5. Calculate the change in tumor burden relative to baseline and the change in tumor burden relative to nadir.

Step 6. Derive the overall response using the table below.

Overall Response	Criterion
irCR	Complete disappearance of all lesions (whether measurable or not, and no new lesions) confirmed by a repeat, consecutive assessment ≥ 4 weeks from the date first documented
irPR	Decrease in tumor burden ≥ 50% relative to baseline confirmed by a consecutive assessment ≥ 4 weeks from the date first documented
irSD	Criteria for irCR, irPR, and irPD are not met; does not require confirmation
irPD	Increase in tumor burden ≥ 25% relative to nadir confirmed by a consecutive assessment ≥ 4 weeks from the date first documented

irCR = immune-related complete response; irPD = immune-related progressive disease; irPR = immune-related partial response; irSD = immune-related stable disease.

DETERMINATION OF irBOR

Once a patient has completed all tumor assessments, his/her irBOR may be determined:

Condition	irBOR
At least one irCR	irCR
At least one irPR and no irCR	irPR
At least one irSD and no irCR and no irPR	irSD
At least one irPD and no irCR, no irPR, and no irSD	irPD

irBOR = immune-related best overall response; irCR = immune-related complete response; irPD = immune-related progressive disease; irPR = immune-related partial response; irSD = immune-related stable disease.

17.7 Appendix 7: Pill Diary for Epacadostat

Protocol Number: UCDCC#271

Patient Name: _____ **Medical Record #**: _____

Cycle#: _____ **Start Date**: _____ **Dose**: _____

Instructions to Patients: For each cycle day, circle AM or PM in the boxes below when you have taken your medication. For missed doses, line through the AM or PM for that time (e.g., ~~AM~~ or ~~PM~~).

Epacadostat – Twice Daily
Epacadostat is an oral agent that should be taken twice daily every day throughout the study period. Epacadostat should be taken in the morning and evening, approximately 12 hours apart without regard to food. If the morning or evening dose is missed by more than 4 hours, that dose should be skipped and the next scheduled dose should be taken at the usual time.

Cycle Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14
	AM	AM	AM	AM	AM	AM	AM	AM	AM	AM	AM	AM	AM	AM
	PM	PM	PM	PM	PM	PM	PM	PM	PM	PM	PM	PM	PM	PM

Cycle Day	15	16	17	18	19	20	21	22	23	24	25	26	27	28
	AM	AM	AM	AM	AM	AM	AM	AM	AM	AM	AM	AM	AM	AM
	PM	PM	PM	PM	PM	PM	PM	PM	PM	PM	PM	PM	PM	PM

Cycle Day	29	30	31	32	33	34	35	36	37	38	39	40	41	42
	AM	AM	AM	AM	AM	AM	AM	AM	AM	AM	AM	AM	AM	AM
	PM	PM	PM	PM	PM	PM	PM	PM	PM	PM	PM	PM	PM	PM

Cycle Day	43	44	45	46	47	48	49	50	51	52	53	54	55	56
	AM	AM	AM	AM	AM	AM	AM	AM	AM	AM	AM	AM	AM	AM
	PM	PM	PM	PM	PM	PM	PM	PM	PM	PM	PM	PM	PM	PM

Cycle Day	57	58	59	60
	AM	AM	AM	AM
	PM	PM	PM	PM

Patient Signature: _____ Date: _____

Date Returned	# of Pills Left	Collector's Initials	Returned to Pharmacy
			Yes or N/A