UCSF Helen Diller Family Comprehensive Cancer Center

NCT#: 03823131

The Trifecta Study: Optimizing Antitumor Immunity Using Tavokinogene Telseplasmid with Electroporation, Pembrolizumab, and Epacadostat in Squamous Cell Carcinoma of the Head and Neck

Protocol Number: CC #172021

Study Drugs: tavokinogene telseplasmid, electroporation, pembrolizumab, epacadostat

Version Number: 8

Version Date: 08/12/2019

IND Number: 18210

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Revision History

Version 1.0	10/22/2017
Version 2.0	12/30/2017
Version 3.0	04/27/2018
Version 4.0	09/06/2018
Version 5.0	01/17/2019
Version 6.0	04/22/2019
Version 7.0	06/25/2019
Version 8.0	08/12/2019

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Protocol Signature Page

Protocol No.: 172021 **Version Date:** 08-12-2019

1. I agree to follow this protocol version as approved by the UCSF Protocol Review Committee (PRC),Committee on Human Research (CHR), and Data Safety Monitoring Committee(DSMC).
2. I will conduct the study in accordance with applicable CHR requirements, Federal regulations, and state and local laws to maintain the protection of the rights and welfare of study participants.
3. I certify that I, and the study staff, have received the requisite training to conduct this research protocol.
4. I have read and understand the information in the Investigators' Brochure (or Manufacturer's Brochure) regarding the risks and potential benefits. I agree to conduct the protocol in accordance with Good Clinical Practices (ICH-GCP), the applicable ethical principles, the Statement of Investigator (Form FDA 1572), and with local regulatory requirements. In accordance with the FDA Modernization Act, I will ensure the registration of the trial on the www.clinicaltrials.gov website.
5. I agree to maintain adequate and accurate records in accordance with CHR policies, Federal, state and local laws and regulations.

UCSF Principal Investigator / Study Chair

_____
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_____ _____
Signature Date

Participating Site(s)

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Principal Investigator	**Site**
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Protocol Signature Page – Participating Sites

Protocol No.:

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Principal Investigator Name:	Principal Investigator Name:
Institution Name:	Institution Name:
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I have read this protocol and agree to conduct the protocol in accordance with Good Clinical Practices (ICH-GCP), the applicable ethical principles, the Statement of Investigator (Form FDA 1572), Institutional Review Board regulations, and all national, state and local laws and/or requirements of the pertinent regulatory requirements.

Principal Investigator	**Site**
Printed Name	Institution Name
Signature	Date

Abstract

Title	The Trifecta Study: Optimizing Antitumor Immunity Using Tavokinogene Telseplasmid with Electroporation, Pembrolizumab, and Epacadostat in Squamous Cell Carcinoma of the Head and Neck
Patient population	Patients with recurrent or metastatic squamous cell carcinoma of the head and neck with tumors that are accessible for injection and electroporation
Rationale for Study	Squamous cell carcinoma of the head and neck (SCCHN) is a major cause of death globally with 380,000 deaths annually[1]. Anti-PD1 antibodies induce durable remissions in only 12-20% of patients with unresectable SCCHN[2,3]. The presence of tumor infiltrating 'partially exhausted' PD-1$^+$ tumor-specific CD8$^+$ T cells and antigen/MHC I complexes on the tumor cell surface appear to be prerequisites for a response with anti-PD1 agents. Down regulation of antigen presentation is a common immune-evasion strategy in tumors, particularly in SCCHN, where impairment of normal pathways of MHC I antigen processing and presentation is observed in up to 50% of tumors. HNSCC patients who lack tumor-infiltrating lymphocytes (TILs) and the associated IFNγ-gene signature are extremely unlikely to respond to anti-PD-1[4]. Interleukin-12 (IL-12) promotes a pro-inflammatory tumor environment, enhancing antigen presentation, Th1 polarization, the frequency of TIL and ultimately productive systemic anti-tumor immune responses. When IL-12 is administered systemically, it can be toxic[5], but intratumoral electroporation of tavokinogene telseplasmid (tavo-EP) leads to sustained IL-12 exposure in the tumor microenvironment, priming immune responses and leading to regression of both treated and untreated lesions in the absence of systemic therapy. In Phase 1 and 2 clinical trials in melanoma and in a pilot study in SCCHN, tavo-EP was shown to be well-tolerated, with one treatment related SAE in monotherapy (1 pt / 96) and one in combination (1pt /23) – both cellulitis[6,7].tavo-EP monotherapy resulted in characteristics associated with an inflamed tumor, including increased presence of TILs and expression of IFNγ-associated pro-inflammatory genes. In a follow-up study, tavo-EP was combined with the PD-1 antibody pembrolizumab in melanoma patients predicted not to respond to pembrolizumab alone based on a flow cytometry assay where a low frequency of partially-exhausted CD8$^+$ T cells in the tumor microenvironment yields a remarkably precise negative predictive value[9]. The BORR to combination therapy in this population was 43%, far higher than anticipated based on both the flow cytometry and an PD-L1 IHC predictive assays[9,9], and durable responses were seen in patients with prior progression on PD-1 antibodies alone[10]. Paired biopsy specimens in responders demonstrated both an increase in TILs and in the ratio of effector T cells to regulatory cells. In contrast, non-responders often

Rationale(continued)	demonstrated an increase in TILs both in treated and untreated lesions, but the balance between effector $CD8^+$ T cells is skewed towards suppressive lymphocytes ($PD\text{-}L1^+CD163^+$ monocytes and $FoxP3^+$ Tregs). In the SCCHN pilot study, lesions in non-responders were often richly infiltrated with TILs suggesting a significant role of regulatory cells in hindering antitumor immunity. Epacadostat is an oral IDO1 inhibitor that increases proliferation and activation of effector cells including NK cells, DCs, and T lymphocytes while depleting Tregs. Clinical data thus far has demonstrated that the combinations of epacadostat and PD-1 Abs and the combination of tavo-EP and PD-1 Abs have been well tolerated. Our data thus far also suggest that effective anticancer immune responses require 3 steps: 1) immune priming and tumor infiltration with T cells; 2) activation of partially exhausted TILs; and 3) selective modulation of T cell populations to maximize the $CD8^+$ T_E : Treg ratio. Based on this framework, we hypothesize that the combination of tavo-EP (step 1) with pembrolizumab (step 2) and epacadostat (step 3) will substantially increase the BORR to pembrolizumab and tavo-EP alone, in patients with squamous cell carcinoma of the head and neck and that this combination will be well tolerated in this population.
Primary Objective	**Dose Escalation Safety Lead-In:** • Assess the safety of tavo-EP and pembrolizumab in combination with epacadostat (CTCAE version 4) **Dose Expansion:** • Determine whether the combination of tavo-EP, pembrolizumab, and epacadostat increases the best overall response rate (BORR) in SCCHN compared with historical data for pembrolizumab monotherapy
Secondary Objectives	**Dose Expansion:** • Determine the durability of clinical benefits in patients treated with tavo-EP, pembrolizumab, and epacadostat as assessed by time to progression, median PFS, median OS

Exploratory Objectives	• Determine whether the combination of tavo-EP, pembrolizumab, and epacadostat increases the objective response rate in SCCHN compared with emerging data for pembrolizumab in combination with epacadostat • Determine the effects of combination therapy on treated and untreated lesions by examining paired biopsy specimens for relative changes in the expression of innate and adaptive immune-specific genes, the density of $CD8^+$effector versus $CD4^+$regulatory TIL, evaluation of systemic inflammatory cytokines, T-cell clonality, and other hallmarks of immune activation. • Interrogate different subsets of PBMC to explore changes in phenotypic markers associated with productive systemic anti-tumor immune responses such as frequencies of short-lived effector cells and memory T cells, activated NK cells and APCs. • Explore treatment-related changes in functional immune responses using ELISpot, intracellular cytokine release and other assays. • To explore biomarkers that inform scientific understanding of this therapeutic treatment through analysis of specimens retained for future biomedical research.

Study Design	This is a multi-center, open label, 2-stage, double-arm, clinical trial in which patients in Stage 1 will receive either tavo-EP with pembrolizumab, and epacadostat (Arm A) or tavo-EP and pembrolizumab (Arm B). Depending on the response from Stage 1, Stage 2 will continue to investigate the arms. **Dose Escalation Safety Lead-In:** *tavo-EP:*pUMVC3-hIL-12-NGVL33 (tavo-EP) will be injected intratumorally on Days 1, 5 and 8 every 6 weeks to up to 7 accessible lesions without exceeding 20 mL per day. Injected lesions will then be electroporated using the ImmunoPulse electroporation device. *Pembrolizumab*: Pembrolizumab will be administered by a 30 minute IV infusion at a dose of 200 mg every 3 weeks. *Epacadostat:* Epacadostat will be administered at a dose of 300mg PO bid, and if well-tolerated, patients will be dose escalated to 600 mg PO bid. Best overall response rate (BORR) by RECIST v1.1 will be compared to historical data for pembrolizumab monotherapy in SCCHN and to emerging data regarding the combination of pembrolizumab and epacadostat. **Stage 1:** *Once the dose for epacadostat has been established in the dose escalation safety lead-in, Stage 1 will begin with the enrollment to both Arms A and B.* *Arm A:* *tavo-EP:*pUMVC3-hIL-12-NGVL33 (tavo-EP) will be injected intratumorally on Days 1, 5 and 8 every 6 weeks to up to 7 accessible lesions without exceeding 20 mL per day. Injected lesions will then be electroporated using the ImmunoPulse electroporation device. *Pembrolizumab*: Pembrolizumab will be administered by a 30 minute IV infusion at a dose of 200 mg every 3 weeks. *Epacadostat:* Epacadostat will be administered at the dose level determined in the dose escalation safety lead-in. *Arm B:* *tavo-EP:*pUMVC3-hIL-12-NGVL33 (tavo-EP) will be injected intratumorally on Days 1, 5 and 8 every 6 weeks to up to 7 accessible lesions without exceeding 20 mL per day. Injected lesions will then be electroporated using the ImmunoPulse electroporation device. *Pembrolizumab*: Pembrolizumab will be administered by a 30 minute IV infusion at a dose of 200 mg every 3 weeks.

	Stage 2: At the conclusion of Stage 1, if there are at least ≥ 3 responses in 15 patients, in either Arms A or B, up to an additional 26 patients (13 patients in Arm A and 13 patients in Arm B) will be enrolled in the respective treatment arms.
Number of patients	The overall study (including dose escalation safety lead-in and dose escalation) plans to enroll up to 68 evaluable patients. Dose Escalation Safety Lead-In: We expect to enroll 12 patients overall in the safety lead-in (minimum of 9) Dose Expansion Phase, Stage 1: We expect to enroll 30 patients in both arms (15 patients in Arm A and 15 patients in Arm B). We will allow patients who were enrolled in the dose escalation safety lead-in to enroll in Arm A of Stage 1, depending on the final dose. Dose Expansion Phase, Stage 2: Depending on the results of the clinical data in Stage 1, Stage 2 will enroll up to an additional 26 patients.

Inclusion Criteria	Patient Characteristics 1. Age ≥ 18 years old; 2. ECOG performance status 0-2; 3. Life expectancy of at least 4 months; Disease Characteristics 4. Patients must have histological or cytological diagnosis of carcinoma of the head and neck that is not amenable to surgical resection or locoregional radiation therapy with curative intent; 5. At least one accessible lesion (AL) for intratumoral injection. An AL is defined as meeting the following criteria; (1) at least 0.3 cm x 0.3 cm in longest perpendicular diameters (2) in a suitable location for application of electroporation. Tumors invading the carotid artery or at other sites that the investigator believes to be at high risk of life-threatening hemorrhage should not be injected and these lesions may not be used to meet the inclusion criterion for injectable lesions 6. Measureable disease as defined by RECIST v1.1; at least one lesion where the longest perpendicular diameter is at least 1.0 cm by clinical measurement; or at least 1.0 cm by radiographic imaging for non-nodal lesions; at least 1.5 cm in short axis by radiographic imaging for malignant lymph nodes; If the biopsied lesions were previously irradiated, they must demonstrate either radiographic or pathological evidence of recurrent or residual disease. It is not necessary that this lesion is also an AL. 7. If patient has known brain metastases, they must have stable neurologic status following local therapy (surgery or radiation) for at least 4 weeks without the use of steroids or on stable or decreasing dose of ≤10 mg daily prednisone (or equivalent), and must be without neurologic dysfunction that would confound the evaluation of neurologic and other AEs (patients with a history of carcinomatous meningitis are not eligible); Treatment History 8. Patients may have had prior chemotherapy or immunotherapy or radiation therapy. Any drug related adverse events identified during prior therapy must be well controlled (typically resolution to ≤ grade 1, OR resolved upon investigator review prior to initiation of this therapy; 9. No systemic antineoplastic therapy may be received by the patient between the time of the biopsy and the first administration of study treatment; Consent for Biopsies 10. Patient must agree to any protocol mandated biopsies of tumor (deemed accessible, safe and appropriate for biopsy by the

	investigator's assessment) and they must allow acquired tissue to be used for biomarker and immunological analysis. Fertility 11. For women of childbearing potential, negative serum or urine pregnancy test within 14 days to the first epacadostat, pembrolizumab, or tavo-EP administration, and use of birth control from 30 days prior to the first epacadostat, pembrolizumab, or tavo-EP administration and 120 days following last day epacadostat, pembrolizumab, or tavo-EP administration 12. Male patients must be surgically sterile, or must agree to use contraception during the study and at least 120 days following the last day of epacadostat, pembrolizumab, or tavo-EP administration.

Exclusion Criteria	Medical History Autoimmune 1. Active autoimmune disease that has required systemic treatment in past 2 years. Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment; Cardiac 2. Congestive heart failure (New York Heart Association Class III to IV); 3. History or presence of an abnormal electrocardiogram (ECG) that, in the investigator's opinion, is clinically meaningful. Screening QTc interval > 480 milliseconds is excluded. In the event that a single QTc is > 480 milliseconds, the subject may enroll if the average QTc for the 3 ECGs is < 480 milliseconds. For subjects with an intraventricular conduction delay (QRS interval > 120 milliseconds), the JTc interval may be used in place of the QTc with sponsor approval. The JTc must be < 340 milliseconds if JTc is used in place of the QTc. Subjects with left bundle branch block are excluded. 4. Uncontrolled or clinically significant conduction abnormalities (e.g., ventricular tachycardia on anti-arrhythmic are excluded), 1st degree AV block or asymptomatic LAFB/RBBB are eligible; 5. Uncontrolled, symptomatic ischemia within 6 months of first dose of study treatment or known myocardial infarction in the previous six months; 6. Patients with electronic pacemakers or defibrillators; Pulmonary 7. Evidence of interstitial lung disease or any history of autoimmune pneumonitis including symptomatic and/or pneumonitis requiring treatment; Oncologic 8. Any other current or previous malignancy within the past 2 years that, in the opinion of the Principal Investigator will interfere with study-specific endpoints; Infectious 9. Evidence of significant active infection (e.g., pneumonia, cellulitis, wound abscess, etc.) requiring systemic therapy at time of study enrolment; 10. Patients with HBV surface antigen positive (HBSAg) must have AST and total bilirubin < 1.5 x ULN AND negative HBV RNA PCR OR on antivirals for HBV AND at least 8 weeks of prior anti-PD1 antibody therapy AND no history ofAST or total bilirubin levels > 1.5 x ULN due to PD-1 antibody therapy. 11. Hepatitis C (HCV RNA [qualitative] is detected). Gastrointestinal

	12. Presence of a gastrointestinal condition that may affect drug absorption. Administration of epacadostat through a feeding tube is permitted. Medications / Medication Reactions 13. Patients receiving systemic steroid therapy for a chronic inflammatory condition. Topical steroids, nasal and inhaled steroids are permitted. Prednisone or equivalent ≤ 10 mg/day is permitted as hormone replacement; higher dosage prednisone should be stopped at least 14 days prior to C1D1;

Exclusion Criteria	Medications / Medication Reactions 14. Subjects receiving Monoamine Oxidase Inhibitors (MAOIs) or drug which has significant MAOI activity (meperidine, linezolid, methylene blue) within the 21 days before screening. 15. Any history of Serotonin Syndrome (SS) after receiving serotonergic drugs. 16. Use of any UGT1A9 inhibitor from screening through follow-up period, including the following: diclofenacc, imipramine, ketoconazole, mefenamic acid, and probenecid. 17. Known allergy or reaction to any component of any study drug formulation. 18. Receipt of live attenuated vaccine within 30 days before the first dose of study treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, Bacillus Calmette-Guérin (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. 19. Subjects receiving Monoamine Oxidase Inhibitors (MAOIs) or drug which has significant MAOI activity (meperidine, linezolid, methylene blue) within the 21 days before screening. Laboratories 20. Screening Laboratory Abnormalities a. Absolute neutrophil count (ANC) < 1.0×10^9/L. b. Platelets < 75×10^9/L. c. Hemoglobin < 9 g/dL or < 5.6 mmol/L (transfusion is acceptable to meet this criterion). d. Serum creatinine ≥ 1.5 × institutional upper limit of normal (ULN) OR measured or calculated creatinine clearance (glomerular filtration rate can also be used in place of creatinine or CrCl) < 50 mL/min for subjects with creatinine levels > 1.5 × institutional ULN. e. AST or ALT > 2.5 × institutional ULN. f. Alkaline phosphatase > 2.5 x ULN. Note: Subjects with 1) bone metastases and GGT < 2.5 x ULN may enroll if the alkaline phosphatase is < 5 × ULN. g. Total bilirubin above 1.5 x the institutional ULN AND conjugated bilirubin ≥ 2.0 × ULN. h. International normalized ratio (INR) or prothrombin time (PT) > 1.5 × ULN. i. Activated partial thromboplastin time (aPTT) > 1.5 × ULN.

Efficacy Endpoints	Primary efficacy endpoint: Best overall response rate (BORR); defined as the percentage of patients who attain a confirmed CR or PR over the trial with the triplet treatment with a 4-week confirmatory scan per RECIST v1.1. Secondary efficacy endpoints: Progression free survival (PFS) is defined as the number of days from the date of enrollment to the date of progression or death regardless of cause. Patients who do not have a documented progression or death will be censored on the date of last assessment. Overall survival (OS) is defined as the number of days from the date of enrollment to the date of death regardless of cause, patients without a death date will be censored on the date last known alive.
Exploratory / Translational Endpoints	Translational analyses are intended to be hypothesis generating. Translational endpoints will be met if there have been significant changes in: • Inflammatory genes expression by Nanostring before and after initiation of treatment on study • The relative proportion of effector versus regulatory T-cells in pre-treatment and post-treatment tumor specimens • Pre-treatment versus post-treatment in cytokine expression, T-cell repertoire, clonality • Pre-treatment versus post-treatment populations of immune cell populations in the peripheral blood including short-lived effector cells (SLECs) and memory T-cells • Pre-treatment versus post-treatment functional immune responses using Elispot analysis • Experimental and statistical methods for these assessments are described in **Appendix 4**.
Safety Endpoints	Safety assessments include AEs (either reported by the patient or observed by the Investigator), concomitant medication use, performance status, vital signs, physical examination, and laboratory assessments. AEs will be graded and reported using CTCAE version 4 and reported descriptively.
Safety Assessment	Clinical evaluations including laboratory and clinical safety assessments will be performed at 3-week intervals for patients who are actively receiving treatment on study. For patients in the follow-up portions of the study who are not actively receiving therapy, evaluations will be performed at 12-week intervals. Safety will be assessed during the study by documentation of adverse events (AEs), clinical laboratory tests, physical examination, vital sign measurements, and Eastern Cooperative Oncology Group (ECOG) performance status.

Dose Escalation Safety Lead-In and Mid-Study Interim Safety Analysis	*Dose Escalation Safety Lead-In* 1. If, at any time, 1 or more of the first 3 safety-evaluable patients experience grade 3 or higher treatment-associated adverse events within the first 30 days of initiation of treatment, then no further patients will be enrolled at the current dose level. 2. After 6 patients have been enrolled on study, enrollment will be halted for 30 days for completion of the dose escalation lead-in safety analysis. If 0-1 patients experience grade 3 or higher treatment-associated adverse events within the first 30 days of initiation of treatment, then additional patients may be enrolled at the next dose level. 3. If enrollment is halted at any time during the lead-in period due to treatment-associated adverse events, the UCSF DSMB will review all available safety data with the Principal Investigator. Based on this review, study discontinuation or reduction of the epacadostat dose may be recommended. No further patients will be enrolled on study without the approval of the DSMB. If the DSMB allows additional patients to enroll, the lead-in period will be repeated at the new dose level with a maximum of 6 additional patients enrolled prior to follow-up safety analysis. At the discretion of the DSMB, patients who are currently on study may continue treatment at the reduced dose level. 4. Patients who discontinue treatment on study within 30 days of initiation of therapy for reasons other than treatment-associated toxicity will be deemed inevaluable for safety and replaced for safety analysis. *Mid-Study Interim Safety Analysis (Stage 1)* Enrollment will also be halted for 30 days for interim safety analyses after a total of 30 safety-evaluable patients have initiated treatment on study in both Arms A and B Patients who discontinue treatment on study within 30 days of initiation of therapy for reasons other than treatment-associated toxicity will be deemed inevaluable for safety and replaced for safety analysis. The study will be discontinued under the following circumstance: 1. On-study occurrence of 3 or more Grade 4 (life threatening) serious adverse events (SAEs) or deaths, which are deemed at least possibly related to the study agent. 2. Based on the review of data the DSMB has serious concerns about the safety of patients on the study. In addition to stopping the study, the DSMB may recommend that the epacadostat dose for all patients be de-escalated for all current and future patients or cessation of further patient accrual.

Duration of Therapy	Dose Escalation Safety Lead-In Phase: 6 patients will receive triplet therapy for 30 days at Dose level 0. After 30 days of therapy, if those patients do not experience a DLT, an additional 6 patients will be enrolled at the next Dose level, Level 1 which will increase epacadostat to 600 mg for 30 days, tavo-EP and pembrolizumab will not be dose escalated. If no patients experience a DLT at 600 mg, that will be the dose level of epacadostat used in Stage 1, for both Arms A and B. Dose Expansion Phase, Stage 1, Arm A: Patients will receive triplet therapy for 12 months or until the development of an unacceptable treatment associated toxicity or confirmed progression. After 12 months of therapy, patients will enter the follow-up phase for the next 24 months. Patients with disease progression during the follow-up phase will have access to 12 additional months of triplet therapy. Patients who are eligible for treatment on study but who have experienced regression of all previously accessible lesions may continue on pembrolizumab and epacadostat without tavo-EP. Dose Expansion Phase, Stage 1, Arm B: Patients will receive combination therapy for 12 months or until the development of an unacceptable treatment associated toxicity or confirmed progression. After 12 months of therapy, patients will enter the follow-up phase for the next 24 months. Dose Expansion Phase, Stage 2: Depending on the results of the clinical data in Stage 1, Stage 2 will enroll up to an additional 26 patients accordingly: If there are at least ≥ 3 responses in 15 patients, in either Arms A or B, up to an additional 26 patients (13 patients in Arm A and 13 patients in Arm B) will be enrolled in the respective treatment arms.
Duration of Follow up	Patients will be followed at 3 month intervals for toxicity and radiographic imaging 1) until start of a new anti-cancer treatment, (2) until 30 days after documented disease progression, (3) until death, or (4) until 36 months from the initiation of treatment on study, whichever comes first. Each subject will be followed for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.
Duration Of Study	Study accrual will be sufficient to assess the primary endpoint within 24 months from the time the study opens to accrual.

Sample Size Justification and Efficacy Assessment	**Sample Size Justification:** Dose Expansion Phase, Stage 1: We expect to enroll 30 patients in both arms (15 patients in Arm A and 15 patients in Arm B). We will allow patients who were enrolled in the dose escalation safety lead-in to enroll in Arm A of Stage 1, depending on the final dose. Dose Expansion Phase, Stage 2: Depending on the results of the clinical data in Stage 1, Stage 2 will enroll up to an additional 26 patients accordingly: If there are at least ≥ 3 responses in 15 patients, in either Arms A or B, up to an additional 26 patients (13 patients in Arm A and 13 patients in Arm B) will be enrolled in the respective treatment arms. The above Simon 2-stage sample sizes were based on the following assumptions: the objective response rate for pembrolizumab is approximately 15%[3] and we suggest that a 20% absolute improvement in this response rate would be clinically meaningful. We propose to test the hypothesis that the objective response rate for the combination of tavo-EP with pembrolizumab and epacadostat is 35% versus the null hypothesis that it is similar to the response rate for pembrolizumab monotherapy, 15%. The statistical power calculations are based on the Simon Two-Stage Optimal Design[11] with a Type I error rate of 0.05 and power of 80%. **Efficacy Assessment:** The objective response rate for pembrolizumab is approximately 15%[3] and we suggest that a 20% absolute improvement in this response rate would be clinically meaningful. We propose to test the hypothesis that the objective response rate for the combination of tavo-EP with pembrolizumab and epacadostat is 35% versus the null hypothesis that it is similar to the response rate for pembrolizumab monotherapy, 15%. The following statistical power calculations are based on the Simon Two-Stage Optimal Design[11] with a Type I error rate of 0.05 and power of 80%.

Statistical consideration	The standard summary statistics for continuous variables are sample size (n), mean, standard deviation (SD), median, minimum and maximum. The standard summary statistics for categorical variables are frequencies and percentages. BORR will calculated as a percentage relative to all patients who received the study therapy, and 95% confidence interval is calculated by the Clopper-Pearson (exact binomial) method. Time to event variables will be summarized using the Kaplan-Meier method. Where confidence limits are appropriate, the confidence level will be 95% (two-sided), as determined by the Brookmeyer and Crowley method, unless otherwise stated. Individual data (including relevant derived variables) will be presented by parameter in listings. Results of statistical analyses, descriptive summary statistics and supportive listings will also be presented. Statistical analyses (and experimental methods) for the exploratory, translational objective are described in **Appendix 4**.

List of Abbreviations

AE	adverse event
AL	accessible lesion
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CBC	complete blood cell (count)
CR	complete response
CRC	Clinical Research Coordinator
CRF	case report form
CT	computerized tomography
CTCEA	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTMS	Clinical Trial Management System
DFS	disease-free survival
DLT	dose limiting toxicity
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ECOG	Eastern Cooperative Oncology Group
EP	Electroporation
FCBP	female of childbearing potential
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBeAg	Hepatitis B “e” antigen
HBV	hepatitis B virus
HCT	hematocrit
HCV	hepatitis C virus
HDFCCC	Helen Diller Family Comprehensive Cancer Center
HGB	hemoglobin
HIV	human immunodeficiency virus
ICH	International Conference on Harmonization
IND	investigational new drug application
IL	interleukin
IP	investigational product
IRB	Institutional Review Board
IRRC	immune related-Response Criteria

List of Abbreviations

IT	intratumoral
IV	intravenous
LDH	lactate dehydrogenase
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI	National Cancer Institute
ORR	Objective response rate
PD	disease progression
tavo-EP	tavokinogene telseplasmid with electroporation
PK	pharmacokinetics
PR	partial response
PRC	Protocol Review Committee (UCSF)
RBC	red blood cell (count)
SAE	serious adverse event
SD	stable disease
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
TIL	tumor infiltrating lymphocytes
TKI	targeted kinase inhibitors
TE AE	treatment emergent adverse event
TR AE	treatment related adverse event
ULN	upper limit of normal
WBC	white blood cell (count)

Table of Contents

1 Introduction

1.1 Background

1.1.1 Squamous cell carcinoma of the head and neck (SCCHN)

While localized and locoregional SCC of the head and neck (HNSCC) can be cured with surgery, radiation, or chemoradiation, a substantial number of patients will develop recurrent or distant metastatic disease after definitive locoregional therapy. These recurrences are associated with a poor overall prognosis[12], and the median overall survival in patients with metastatic SCC of the head and neck is under a year even with intensive combination chemotherapy[13]. The addition of monoclonal antibodies targeting the epidermal growth factor receptor (EGFR) to chemotherapy improves these outcomes somewhat, but these multi-agent combinations often induce significant treatment-associated toxicity that negatively impacts quality of life. As a result of the limited efficacy of standard of care treatment options, 11,500 patients die every year from squamous cell carcinoma of the oral cavity and the oropharynx in the United States alone[14].

1.1.2 FDA approved immunotherapy in SCCHN

1.1.2.1 Anti-PD1 Antibodies

The anti PD-1 antibodies pembrolizumab and nivolumab have been approved by the FDA for the treatment of chemotherapy refractory recurrent / metastatic SCCHN. Although these agents can induce durable, objective tumor responses in both HPV positive and HPV negative tumors, response rates are low, ranging from 12-18%[2,3]. Anti-PD-1 antibodies have been well tolerated with only 1 in 8 SCCHN patients experiencing grade 3 or higher adverse events. PD-1 and PD-L1 treatment failures in advanced solid tumors have been associated with inadequate intratumoral inflammatory immune responses[15] and an excess of regulatory cells in the tumor microenvironment[10].

1.2 Investigational Agents

1.2.1 tavo-EP

tavo-EP: Background

Tavokinogene telseplasmid with electroporation (tavo-EP) is a gene therapy approach to inducing stable intratumoral expression of the pro-inflammatory cytokine IL-12. Interleukin-12 (IL-12) is anan endogenous, 70 kilodalton protein consisting of two subunits linked by a disulfide bond[16]. It is a potent pleotropic cytokine, capable of driving cell-mediated immunity through multiple parallel mechanisms, including activation of NK cells and cytotoxic T lymphocytes (CTLs) as well as inhibition of regulatory T cells and myeloid-derived suppressor cells (MDSCs)[16–18]. Also, as a potent inducer of interferon-gamma (IFN-□□, IL-12 can drive upregulation of antigen processing and presentation machinery (APM) within tumors.

tavo-EP: Pre-Clinical Data

For a thorough discussion of the pharmacology and preclinical background of tavokinogene telseplasmid, refer to the tavo Investigator's Brochure, Section 4.0

Clinical trials of tavo-EP monotherapy

tavo-EP: Safety

Overall, 96 patients (5 patients with squamous cell carcinoma of the head and neck) have been treated with monotherapy tavo-EP. In general, treatment has been well tolerated and transient,

grade 3 procedural pain has been the only observed grade 3 or higher adverse event. A summary of all grade treatment associated AEs seen in over 5% of patients and all grade 3 or higher AEs (N = 96) is given in **Table 1-1**.One SAE potentially related to monotherapy was cellulitis in one patient (1/96) that resolved with antibiotics. Additionally, one patient with head and neck cancer died from a tumoral bleeding episode involving a lesion that was distant from any treatment site. The patient's death was unrelated to treatment on study in the opinion of the treating investigator.

Table 1-1All grade treatment associated AEs seen in over 5% of patients and all grade 3 or higher AEs (N = 96)

Category	Adverse Reaction	Gr 1-2	Gr 3-4	Grade 5	All Grades
Reactions at Treatment Site	Procedural Pain	47.9%	5.2%	-	53.1%
	Inflammation	12.5%	-	-	12.5%
	Discoloration	11.5%	-	-	11.5%
	Bruising	5.2%	-	-	5.2%
Skin	Pruritus	5.2%	-	-	5.2%
	Cellulitis	5.2%	2.6%	-	5.2%
Constitutional	Fatigue	5.2%	-	-	5.2%
Any Related AE		*61.5%*	*5.2%*	-	*66.7%*

tavo-EP: Safety Data in SCCHN

In a pilot / feasibility study, four patients with SCCHN were administered at least 1 cycle of intratumoral TAVO EP, with one participant receiving 9 cycles of treatment. Of the 4 participants enrolled in the study, 1 participant completed the study, 2 had progressive disease and 1 died from disease.

Treatment with intratumoral TAVO EP had an acceptable safety profile and was well tolerated (**Table 1-2**). There was 1 death during the study, which was reported as a serious adverse event (SAE), however, this event was not related to intratumoral TAVO EP, but as a result of disease progression. For this patient, treatment was restricted to a superficial subcutaneous lesion on the left anterior neck. The patient received a total volume of 0.55 mL of plasmid IL-12 at a concentration of 0.5 mg/mL. Approximately 33 days after cycle one day one and approximately 18 days since his most recent treatment (cycle 1 day 15), the patient presented to the emergency department with uncontrolled bleeding from a tumor that was on the contralateral side of his neck (right medial neck). This lesion had grown in size during the course of study and the episode was attributed to disease progression.

There were 3 participants who experienced study drug-related TEAEs, including procedural pain, bruising, or bleeding. There were no TEAEs leading to study drug withdrawal.

Table 1-2Treatment-emergent adverse events (AEs) regardless of attribution.

System Organ Class Preferred Term	All Events n (%)[a]	≥ Grade 3[b] n (%)[a]
Patients Reporting Any TEAE	4 (100%)	1 (25.0%)
Gastrointestinal disorders	1 (25.0%)	0
Nausea	1 (25.0%)	0
General disorders and administration site conditions	2 (50.0%)	0
Injection site bruising	1 (25.0%)	0
Injection site haemorrhage	1 (25.0%)	0
Infections and infestations	1 (25.0%)	0
Cellulitis	1 (25.0%)	0
Injury, poisoning and procedural complications	2 (50.0%)	0
Procedural pain	2 (50.0%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (25.0%)	1 (25.0%)
Tumour haemorrhage	1 (25.0%)	1 (25.0%)
Nervous system disorders	1 (25.0%)	0
Paraesthesia	1 (25.0%)	0
Skin and subcutaneous tissue disorders	1 (25.0%)	0
Skin lesion	1 (25.0%)	0

tavo-EP: Efficacy in Melanoma

Intratumoral injection of tavo-EP is currently under investigation in metastatic melanoma. A Phase I trial in melanoma was conducted involving seven dosing cohorts with a total of 24 patients. Patients received one cycle consisting of three days of treatment. Maximum total plasmid injected per visit ranged from 0.2-6 mg, at concentrations ranging from 0.1-1.6 mg/mL. A dose proportional increase in IL-12 protein expression compared to pretreatment in biopsied tumors was seen in all patients with no significant IL-12 spillage into circulation. Most (76%) electroporated lesions demonstrated greater than 20% necrosis at the time of follow-up biopsy or excision performed between 3 and 31 days after the last injection. Four of 19 patients who had distant disease had evidence of distant responses including 3 complete responses in patients with progressive metastatic disease. Of these patients, 2 patients had not had any subsequent systemic therapy while 1 patient had received dacarbazine following tavo-EP therapy. All three complete responses occurred in the setting of patients with disseminated progressive cutaneous lesions. No dose related or treatment related toxicity was seen except for transient pain and discomfort at the injection site[22].

In a3 part, phase II multicenter study of intratumoral tavo-EP (0.5 mg/mL) in subjects with in-transit or cutaneous melanoma, the primary objectives of the first two study parts (Main and Addendum) were to assess the overall response rate (CR + PR) by either investigator modified skin Response Evaluation Criteria in Solid Tumors (msRECIST) or derived msRECIST. The trial has enrolled 51 subjects (Main =30, Addendum = 21). Efficacy data with tavo-EP as monotherapy with different dosing regimens showed a best overall response rate (BORR) of 25% to 34% as

well as 38.5 to 50.0% observed regression of distal untreated lesions. Moreover, subjects who received intratumoral tavo-EP and later went on to receive an anti-PD-1 antibody demonstrated a high PD-1-associated response rate (64% complete response [CR] + partial response [PR]). Interestingly, subjects who received an anti PD-1 antibody with no intervening therapy post intratumoral tavo-EP had a BORR of 75% (CR+PR).

Clinical data for tavo-EP in combination with pembrolizumab

Safety

Intratumoral tavo-EP was administered in combination with pembrolizumab in 22 advanced melanoma patients as part of a phase 2 clinical trial. The only grade 3 or higher adverse events observed were treatment site reactions and, in 1 patients, a transient grade 3 AST elevation. All adverse events seen in > 10% of patients treated with tavo-EP in combination with pembrolizumab and all grade 3+ AEs (N = 22) are given in **Table 1-3**.

Table 1-3All AEs seen in > 10% of patients treated with tavo-EP in combination with pembrolizumab and all grade 3+ AEs (N = 22)

Category	*Adverse Reaction*	*Grade 1-2*	*Grade 3-4*	*Grade 5*	*All Grades*
Reactions at Treatment Site	Pain	45.5%	9.1%	-	54.5%
	Cellulitis	-	4.5%	-	4.5%
Skin	Pruritus	22.7%	-	-	22.7%
	Rash	18.2%	-	-	18.2%
Constitutional	Fatigue	63.6%	-	-	63.6%
Respiratory	Cough	13.6%			13.6%
Gastrointestinal	Nausea	31.8%	-	-	31.8%
	Diarrhea	13.6%	-	-	13.6%
	Constipation	13.6%			13.6%
Musculoskeletal	Myalgia	22.7%	-	-	22.7%
	Arthralgia	13.6%	-	-	13.6%
	Peripheral Edema	13.6%	-	-	13.6%
Neurological	Dizziness	27.3%	-	-	27.3%
	Headache	18.2%	-	-	18.2%
Labs	Increased AST	4.5%	4.5%	-	9.1%
	Increased Creatinine	13.6%	-	-	13.6%

tavo-EP: Efficacy in Melanoma in combination with aPD-1

The ongoing combination therapy study (tavo-EP with pembrolizumab; CC 15852/OMS I102) in subjects with low TILs showed a BORR of 50% (11/22); a CR of 41% (9/22); a disease control rate (DCR; CR + PR + stable disease [SD]) of 59% (13/22); progression free survival (PFS) of 57% at 15 months; and duration of response (DOR) of 100% (11/11) (Algazi, Tsai et al. 2016; Algazi, Tsai et al. 2016 AACR; Algazi 2017). These results are highly promising, since the eligible population are predicted to not responder to anti-PD-1 therapy alone.

1.2.2 Epacadostat

IDO Background

Inhibition of Indoleamine 2,3-Dioxygenase 1 as a Target for Cancer

Recent interest has focused on the role of IDO1 as a mechanism of induction of tolerance to malignancy[24]. Indoleamine 2,3-dioxygenase 1 is a heme-containing, monomeric oxidoreductase that catalyzes the degradation of the essential amino acid tryptophan to N-formyl-kynurenine. Kynurenine can be subsequently metabolized through a series of enzymatic steps to nicotinamide adenine dinucleotide. Indoleamine 2,3-dioxygenase 1 is the first rate-limiting enzyme in one of the breakdown pathways of tryptophan. In another pathway, tryptophan hydroxylase catalysis of tryptophan leads to the formation of serotonin and melatonin.

The expression and activity profiles of IDO1 are distinct from those of tryptophan dioxygenase, an enzyme predominantly expressed in liver that catalyzes the same enzymatic reaction as IDO1 and maintains proper tryptophan balance in response to dietary uptake. In contrast to tryptophan dioxygenase, IDO1 is expressed in a variety of tissues, with particularly high levels found in areas of contact with potential sources of immune challenge (eg, gut, respiratory tract, placenta, spleen), consistent with a role for regulating tryptophan metabolism in a local microenvironment[25]. Within the immune system, IDO1 activity is specifically induced in cells such as DCs and macrophages at localized sites of inflammation[26].

Indoleamine 2,3-dioxygenase 1–driven oxidation of tryptophan results in a strong inhibitory effect on the development of T-cell–mediated responses by blocking T-cell activation and inducing T-cell apoptosis[27]. Both the reduction in local tryptophan levels and the production of tryptophan catabolites that are inhibitory to cell proliferation contribute to the immunosuppressive effects[28]. Indoleamine 2,3-dioxygenase 1 activity also promotes the differentiation of naive T cells to cells with a regulatory phenotype (Treg)[29]. Because increased Treg activity has been shown to promote tumor growth and Treg depletion has been shown to allow an otherwise ineffectual antitumor immune response to occur[30], IDO1 expansion of Treg may provide an additional mechanism whereby IDO1 could promote an immunosuppressive environment.

The biological relevance of IDO1 inhibition to immune tolerance was first demonstrated when it was shown that treating mice with a small molecule inhibitor of the IDO1 pathway, 1 methyl tryptophan, could break the tolerogenic state that protects the allogeneic conceptus from the maternal immune system[31]. A critical role for IDO1 in immunomodulation has been confirmed in numerous animal models, including models of allograft tolerance, inflammation, and cancer[25]. While IDO1 inhibition can exacerbate disease in models of autoimmune disorders[25], IDO1 null mice show no evidence of susceptibility to developing spontaneous autoimmunity or alterations in immune system development[27], suggesting that IDO1 inhibition, in a therapeutic setting, may produce minimal side effects in subjects without pre-existing autoimmune conditions.

Within the context of cancer, there are several lines of evidence to suggest that IDO1 is a key regulator of the immunosuppressive mechanisms responsible for tumor escape from immune surveillance. Several groups have demonstrated that blockade of IDO1 activity can directly influence the ability of tumor-bearing animals to reject tumors[32,33]. In addition, studies with 1-methyl-tryptophan demonstrate that IDO1 inhibition dramatically increases the efficacy of various chemotherapeutic agents (eg, platinum compounds, taxane derivatives, cyclophosphamide) without increased toxicity[33]. Although the specific mechanisms responsible for this potentiation remain to be fully elucidated, the effects were not observed in T-cell–deficient animals, suggesting

that the results may be the consequence of the disablement of immunosuppressive mechanisms that exist within the tumor microenvironment.

Based on studies examining serum levels of tryptophan and kynurenine, IDO1 appears to be chronically activated in patients with cancer, and IDO1 activation correlates with more extensive disease[34,35]. Indoleamine 2,3-dioxygenase 1 has subsequently been found to be overexpressed by a wide variety of human tumor cell types, as well as by the DCs that localize to the tumor-draining lymph nodes[25,32]. Increased expression of IDO1 in tumor cells has been shown to be an independent prognostic variable for reduced overall survival (OS) in subjects with melanoma, ovarian, colorectal, and pancreatic cancers[36–40].

Together, these results suggest that the IDO1 pathway is a key regulatory element responsible for the induction and maintenance of tumor immune tolerance. Small molecule inhibitors of IDO1 may provide an innovative and tractable method to treat malignancies either alone or in combination with chemotherapeutics and/or immunotherapy-based strategies.

EPACADOSTAT: BACKGROUND

Mechanism of Action

Epacadostat represents a novel, potent, and selective inhibitor of the enzyme indoleamine 2,3-dioxygenase 1 (IDO1) in both human tumor cells and human dendritic cells (DCs).

Pharmaceutical and Preclinical Background

For a thorough discussion of the pharmacology and preclinical background of epacadostat, refer to the epacadostat Investigator's Brochure, Sections 3.0 and 4.0

Epacadostat: Clinical safety data

Combination Therapy

As of the data cut off (28 MAR 2016), 60 subjects have been enrolled in INCB 24360-202 (epacadostat 25 mg, 50 mg, 100 mg, and 300 mg BID in combination with pembrolizumab). Based on the preliminary unaudited safety data (unaudited), no Grade 4 treatment related AEs were reported. Three subjects (5%) discontinued for a treatment-related AE: Grade 3 arthralgia, Grade 3 AST elevation, and Grade 2 nervous system disorder. No treatment-related deaths occurred. Treatment-emergent AEs were reported in 44 subjects (73.0%). The most frequently reported AEs were rash (27%) followed by fatigue (23%). Rash includes the preferred terms rash, rash generalized, rash maculopapular, rash pruritic, and rash follicular. As of the data cutoff (28 MAR 2016), 18 subjects in the Phase 1 portion of the INCB 24360-202 study and 119 subjects in the Phase 2 portion of the study have received combination treatment with pembrolizumab and the 100 mg BID dose of epacadostat, the recommended dose for the Phase 3 study. The data for Phase 2 presents a subset of 99 subjects who had at least 1 month of safety data. The most frequently reported (≥ 15%) AEs of any grade for the combined Phase 1 and Phase 2 subjects treated with epacadostat 100 mg BID were fatigue (35.0%), constipation (24.8%), diarrhea (20.5%), nausea (20.5%), vomiting (18.8%), pyrexia (16.2%), and dyspnea (15.4%). Fatigue (13.7%) and rash (11.1%; including the preferred terms rash, rash maculopapular, rash generalized, and rash macular) were the only treatment-related AEs reported in > 10% of subjects. Treatment-related AEs of rash were only reported in Phase 2. Treatment-related AEs ≥ Grade 3 occurring in more than 1 subject who received epacadostat 100 mg BID in Phase 1 or Phase 2 included rash (5 subjects, 4.3%) and dehydration, lipase increased, AST increased, and nausea (2 subjects [1.7%] each).

For a thorough discussion of the pharmacology and preclinical background of epacadostat, refer to the epacadostat Investigator's Brochure, Sections 6.0 and 7.0

Clinical efficacy data for epacadostat in combination with pembrolizumab in HNSCC

Efficacy

Epacadostat was tested in combination with the PD-1 antibody pembrolizumab in 38 patients with SCCHN as part of a phase 1 / 2 clinical trial. Objective responses were seen in 11 of 36 evaluable patients (30.5%) and disease stabilization was observed in 10 additional patients for an overall disease control rate of 58.3%[17].

Rationale for the Proposed Study

Anti-PD1 antibodies induce durable remissions in only 12-20% of patients with unresectable SCCHN[2,3]. HNSCC patients, who lack tumor-infiltrating lymphocytes (TILs) and the associated IFN-γ-gene signature are extremely unlikely to respond to anti-PD-1[4]. Interleukin-12 (IL-12) promotes a pro-inflammatory tumor environment, enhanced antigen presentation, Th1 polarization, an increased frequency of TIL and ultimately productive systemic anti-tumor immune responses. When IL-12 is administered systemically, it can be toxic[5], but intratumoral electroporation of plasmid IL-12 (tavokinogene telseplasmidor tavo-EP) leads to sustained IL-12 exposure in the tumor microenvironment, priming immune responses and leading to regression of both treated and untreated lesions in the absence of systemic therapy. tavo-EP demonstrates substantial clinical synergy with the PD-1 antibody, pembrolizumab, and even non-responders often demonstrated an increase in TILs both in treated and untreated lesions. However, the balance between effector $CD8^+$ T cells is skewed towards suppressive leukocytes ($PD\text{-}L1^+CD163^+$ monocytes and $FoxP3^+$ Tregs) in non-responders. Epacadostat is an oral IDO1 inhibitor that increases proliferation and activation of effector cells including NK cells, DCs, and T lymphocytes while depleting Tregs. Our data thus far also suggest that effective anticancer immune responses require 3 steps: 1) immune priming and tumor infiltration with T cells; 2) activation of partially exhausted TILs; and 3) selective modulation of T cell populations to maximize the $CD8^+$ T_E : Treg ratio. Based on the results of the clinical and translational data in Stage 1, Stage 2 will be developed in consultation with the Principal Investigator and leadership from both OncoSec and Incyte. Which will be submitted to the local and federal regulatory bodies for review and approval prior to being implemented.

2 Objectives of the Study

2.1 Primary

Dose Escalation Safety Lead-In:

- Assess the safety of tavo-EP and pembrolizumab in combination with epacadostat (CTCAE version 4)

Dose Expansion:

- Determine whether the combination of tavo-EP, pembrolizumab, and epacadostat increases the best overall response rate (BORR) in SCCHN compared with historical data for pembrolizumab monotherapy

2.2 Secondary

Dose Expansion:

- Determine the durability of clinical benefits in patients treated with tavo-EP, pembrolizumab, and epacadostat as assessed by time to progression, median PFS, median OS

2.3 Exploratory Objectives

- Determine whether the combination of tavo-EP, pembrolizumab, and epacadostat increases the objective response rate in SCCHN compared with emerging data for pembrolizumab in combination with epacadostat
- Determine the effects of combination therapy on treated and untreated lesions by examining paired biopsy specimens for changes in inflammatory gene expression, relative proportion of effector versus regulatory T cells, evaluation of inflammatory cytokines, T-cell activation, clonality, and other hallmarks of immune activation.
- Explore systemic markers of immune activation by examining circulating T-cell populations for changes in the frequency and effector function of short-lived effector cells and memory T cells.
- Explore changes in functional immune responses using Elispot and other assays.
- To explore biomarkers that inform scientific understanding of this therapeutic treatment through analysis of specimens retained for Future Biomedical Research.

2.4 Endpoints

Primary Endpoint

Dose Escalation Safety Lead-In:

- Adverse events by CTCAE version 4.0. Safety assessments include AEs (either reported by the patient or observed by the Investigator), concomitant medication use, performance status, vital signs, physical examination, and laboratory assessments. AEs will be graded and reported using CTCAE version 4 and reported descriptively.

Dose Expansion:

- Best overall response rate (BORR) by RECIST version 1.1 compared to single agent pembrolizumab. BORR is defined as the percentage of patients who attain a confirmed CR or PR over the trial with the combination treatment with a 4-week confirmatory scan per RECIST v1.1.

2.4.2 Secondary Endpoints

- Median overall survival and progression free survival. Progression free survival (PFS) is defined as the number of days from the date of enrollment to the date of progression or death regardless of cause. . Patients who do not have a documented progression or death will be censored on the date of last assessment. Overall survival (OS) is defined as the number of days from the date of enrollment to the date of death regardless of cause, patients without a death date will be censored on the date last known alive.

2.4.3 Exploratory and Translational Endpoints

Best overall response rate compared to emerging data for pembrolizumab in combination with epacadostat once historical comparison data for the doublet become available.

Translational analyses are intended to be hypothesis generating. Translational endpoints will be met if there have been significant changes in:

- Inflammatory genes expression by Nanostring before and after initiation of treatment on study
- The relative proportion of effector versus regulatory T-cells in pre-treatment and post-treatment tumor specimens
- Pre-treatment versus post-treatment in cytokine expression, T-cell repertoire, clonality
- Pre-treatment versus post-treatment populations of immune cell populations in the peripheral blood including short-lived effector cells (SLECs) and memory T-cells
- Pre-treatment versus post-treatment functional immune responses using Elispot analysis

The experimental methods and statistical analysis plans for these endpoints are described in Appendix 4TranslationalMedicine Methods and Statistical Analysis**Appendix 4**.

3 Study Design

3.1 Characteristics

This is a multi-center, open label, 2-stage, double-arm, clinical trial in which patients in Stage 1 will receive either tavo-EP with pembrolizumab, and epacadostat (Arm A) or tavo-EP and pembrolizumab (Arm B). Based on the results of the clinical data in Stage 1, Stage 2 enroll up to an additional 26 patients.

3.2 Number of Subjects

This trial is planned for up 68 evaluable patients.

3.3 Eligibility Criteria

Patients must have baseline evaluations performed prior to the first dose of epacadostat, pembrolizumab, or tavo-EP and must meet all inclusion and exclusion criteria. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to enrollment. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

3.3.1 Inclusion Criteria

<u>Patient Characteristics</u>

1. Age ≥ 18 years old;
2. ECOG performance status 0-2;
3. Life expectancy of at least 4 months;

Disease Characteristics

4. Patients must have histological or cytological diagnosis of carcinoma of the head and neck that is not amenable to surgical resection or locoregional radiation therapy with curative intent;
5. At least one accessible lesion (AL) for intratumoral injection. An AL is defined as meeting the following criteria; (1) at least 0.3 cm x 0.3 cm in longest perpendicular diameters (2) in a suitable location for application of electroporation. Tumors invading the carotid artery or at other sites that the investigator believes to be at high risk of life-threatening hemorrhage should not be injected and these lesions may not be used to meet the inclusion criterion for injectable lesions
6. Measureable disease as defined by RECIST v1.1; at least one lesion where the longest perpendicular diameter is at least 1.0 cm by clinical measurement; or at least 1.0 cm by radiographic imaging for non-nodal lesions; at least 1.5 cm in short axis by radiographic imaging for malignant lymph nodes; If the biopsied lesions were previously irradiated, they must demonstrate either radiographic or pathological evidence of recurrent or residual disease. It is not necessary that this lesion is also an AL.
7. If patient has known brain metastases, they must have stable neurologic status following local therapy (surgery or radiation) for at least 4 weeks without the use of steroids or on stable or decreasing dose of ≤10 mg daily prednisone (or equivalent), and must be without neurologic dysfunction that would confound the evaluation of neurologic and other AEs (patients with a history of carcinomatous meningitis are not eligible);

Treatment History

8. Patients may have had prior chemotherapy or immunotherapy or radiation therapy. Any drug related adverse events identified during prior therapy must be well controlled (typically resolution to ≤ grade 1, OR resolved upon investigator review prior to initiation of this therapy;
9. No systemic antineoplastic therapy may be received by the patient between the time of the biopsy and the first administration of study treatment;

Consent for Biopsies

10. Patient must agree to any protocol mandated biopsies of tumor (deemed accessible and safe for biopsy by the investigator's assessment) and they must allow acquired tissue to be used for biomarker analysis.

Fertility

11. For women of childbearing potential, negative serum or urine pregnancy test within 14 days to the first epacadostat, pembrolizumab, or tavo-EP administration, and use of birth control from 30 days prior to the first epacadostat, pembrolizumab, or tavo-EP administration and 120 days following last day of epacadostat, pembrolizumab, or tavo-EP administration;
12. Male patients must be surgically sterile, or must agree to use contraception during the study and at least 120 days following the last day of epacadostat, pembrolizumab, or tavo-EP administration.

3.3.2 Exclusion Criteria

Medical History

Autoimmune

1. Active autoimmune disease that has required systemic treatment in past 2 years. Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment;

Cardiac

2. Congestive heart failure (New York Heart Association Class III to IV);
3. History or presence of an abnormal electrocardiogram (ECG) that, in the investigator's opinion, is clinically meaningful. Screening QTc interval > 480 milliseconds is excluded. In the event that a single QTc is > 480 milliseconds, the subject may enroll if the average QTc for the 3 ECGs is < 480 milliseconds. For subjects with an intraventricular conduction delay (QRS interval > 120 milliseconds), the JTc interval may be used in place of the QTc with sponsor approval. The JTc must be < 340 milliseconds if JTc is used in place of the QTc. Subjects with left bundle branch block are excluded.
4. Uncontrolled or clinically significant conduction abnormalities (e.g., ventricular tachycardia on anti-arrhythmic are excluded), 1st degree AV block or asymptomatic LAFB/RBBB are eligible;
5. Uncontrolled, symptomatic ischemia within 6 months of first dose of study treatment or known myocardial infarction in the previous six months;
6. Patients with electronic pacemakers or defibrillators;

Pulmonary

7. Evidence of interstitial lung disease or active, noninfectious pneumonitis including symptomatic and/or pneumonitis requiring treatment;

Oncologic

8. Any other current or previous malignancy within the past 2 years that, in the opinion of the Principal Investigator will interfere with study-specific endpoints;

Infectious

9. Evidence of significant active infection (e.g., pneumonia, cellulitis, wound abscess, etc.) requiring systemic therapy at time of study enrolment;
10. Hepatitis B – Most NPC patients have been infected with hepatitis B (Cancer Epidemol Biomarkers Prev. 2015. 24:1766-73, N = 711) and, therefore, the inclusion of healthy patients with a history of hepatitis B is a central part of this study. In addition, PD-1 antibodies have been proven to be safe in patients with active hepatitis and hepatocellular carcinoma (e. g. KEYNOTE 224). However, patients with HBV surface antigen positive (HBSAg) must have AST and total bilirubin < 1.5 x ULN AND:
11. Negative HBV RNA PCR OR;
12. On antivirals for HBV AND at least 8 weeks of prior anti-PD1 antibody therapy AND no history of AST or total bilirubin levels > 1.5 x ULN due to PD-1 antibody therapy
13. Hepatitis C (HCV RNA [qualitative] is detected).

Gastrointestinal

14. Presence of a gastrointestinal condition that may affect drug absorption. Administration of epacadostat through a feeding tube is permitted.

Medications / Medication Reactions

15. Patients receiving systemic steroid therapy for a chronic inflammatory condition. Topical steroids, nasal and inhaled steroids are permitted. Prednisone or equivalent ≤ 10 mg/day is permitted as hormone replacement; higher dosage prednisone should be stopped at least 14 days prior to C1D1;
16. Receipt of live attenuated vaccine within 30 days before the first dose of study treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, Bacillus Calmette-Guérin (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.
17. Subjects receiving Monoamine Oxidase Inhibitors (MAOIs) or drug which has significant MAOI activity (meperidine, linezolid, methylene blue) within the 21 days before screening.
18. Any history of Serotonin Syndrome (SS) after receiving serotonergic drugs.
19. Use of any UGT1A9 inhibitor from screening through follow-up period, including the following: diclofenac, imipramine, ketoconazole, mefenamic acid, and probenecid.
20. Known allergy or reaction to any component of epacadostat, pembrolizumab, or tavo-EP formulation.

Laboratories

21. Screening Laboratory Abnormalities
    a. Absolute neutrophil count (ANC) < 1.0×10^9/L.
    b. Platelets < 75×10^9/L.
    c. Hemoglobin < 9 g/dL or < 5.6 mmol/L (transfusion is acceptable to meet this criterion).
    d. Serum creatinine ≥ 1.5 × institutional upper limit of normal (ULN) OR measured or calculated creatinine clearance (glomerular filtration rate can also be used in place of creatinine or CrCl) < 50 mL/min for subjects with creatinine levels > 1.5 × institutional ULN.
    e. AST or ALT > 2.5 × institutional ULN.
    f. Alkaline phosphatase > 2.5 x ULN. Note: Subjects with 1) bone metastases and GGT < 2.5 x ULN may enroll if the alkaline phosphatase is < 5 × ULN.
    g. Total bilirubin above 1.5 x the institutional ULN AND conjugated bilirubin ≥ 2.0 × ULN.
    h. International normalized ratio (INR) or prothrombin time (PT) > 1.5 × ULN.
    i. Activated partial thromboplastin time (aPTT) > 1.5 × ULN.

Table 3-1: Study Calendar

Period/Procedure	Screening	Cycle 1 (42 days)				Cycle 2+ (42 days)				Safety Follow-Up
Study Day/Visit Day	**-28 to 0**	**1**	**5**	**8**	**22**	**1**	**5**	**8**	**22**	**30 days from Last Dose**
Informed Consent										
Informed consent	X									
Clinical Procedures										
Medical history[1]	X									
Medication review	X	X			X	X			X	X
Physical exam	X	X			X	X			X	X
Vital signs[2]	X	X	X	X	X	X	X	X	X	X
Performance status[3]	X	X			X	X			X	X
AE assessment[4]		X			X	X			X	X
Treatment: Dose Escalation Safety Lead-In and Stage 1 and Stage 2, Arm A										
tavo-EP		X	X	X		X	X	X		
Pembrolizumab		X			X	X			X	
epacadostat	Continuous oral or per G-tube dosing									
Treatment: Stage 1 and Stage, Arm B										
tavo-EP		X	X	X		X	X	X		
Pembrolizumab		X			X	X			X	
Biospecimen Collections										
Screening Labs[5]	X									
Safety Labs[6]		X			X	X			X	X
ECG[7]	X					(X)				
Archival Specimen Collection	X									
Fresh biopsy[8]	X					X				X
Research Blood (mandatory)[9]		X				X				X
Research Blood (optional)[9]						X			X	
Tumor Assessments										
Tumor measurements[10]	X					(X)				

[1] Medical history includes any conditions resolved within 6 months of enrollment as well as surgeries and therapies related to the treatment of melanoma and any residual toxicity.

[2] Includes blood pressure (systolic and diastolic), respiratory rate, heart rate and temperature. Height only required at screening. Weight only required at screening and day 1 of each cycle.

[3] ECoG

[4] CTCAE version 4

[5] Screening labs include CBC with platelets and differential, LFTs (AST, ALT, total bilirubin, alkaline phosphatase), PT, PTT, electrolytes, BUN, creatinine, glucose, ionized calcium, lipase, amylase, HBsAg, HCV RNA quantitative

[6] Safety labs include CBC with platelets and differential, LFTs (AST, ALT, total bilirubin, alkaline phosphatase), electrolytes, BUN, creatinine, glucose, ionized calcium, lipase, amylase

[7] ECGs will be performed at screening and on day 1 of each odd numbered cycle excluding cycle 1.

[8] Fresh biopsy collection will be done at screening, Cycle 2 Day 1, and at progression/end of treatment. Additional biopsies may be performed if clinically indicated.

[9] Research blood requirements are described in *Section 10*. Mandatory blood collection will occur on Cycle 2, Day 1; Optional sample collection will occur on Day 22 for Cycles 2 and beyond and then on Day 1 for Cycles 3 and beyond. Additional research blood acquisition, storage, and distribution information in provided in *Section 10*. Every effort shall be made to collect mandatory post-treatment (follow-up) research blood samples, but failure to collect this sample due to patient refusal or logistical constraints shall not constitute a protocol deviation or violation.

[10] MRI, contrast-enhanced CT, or PET/CT imaging of the face, neck, chest, abdomen, and pelvis are required at screening and on day 1 of each odd-numbered cycle excluding cycle 1. Both clinical and radiographic measurements may be used. All superficial, clinically apparent lesions that cannot be adequately assessed radiographically (e. g. subcutaneous lesions) must be numbered and photographed with a metric ruler visible in each photograph. For photographed lesions with borders that are not clearly visible, investigators should trace the lesions' outline, making a solid line with a felt-tipped pen. Visible lesions should never be circled with a solid line but dashed or dotted lines may be used to distinguish these markings from the borders of otherwise invisible lesions. Tumor assessments will be made using RECIST version 1.1. IL-12 plasmid dosing may be based on the most recent tumor measurements and measurements need not be repeated immediately prior to each tavo-EP treatment.

[11] Epacadostat dose may be changed if indicated based on dose escalation safety run-in described below in Table 4-1.

3.4 Schedule of Procedures and Observations

The study-specific assessments are detailed in this section and outlined in **Table 3-1: Study Calendar**. Screening assessments must be performed within 28 days prior to the first dose of investigational product unless otherwise noted. Any results falling outside of the reference ranges may be repeated at the discretion of the investigator. All on-study visit procedures are allowed **a window of ± 3 days** unless otherwise noted. Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation.

A written, signed, informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated. A copy of the signed ICF will be given to the subject and a copy will be filed in the medical record. The original will be kept on file with the study records. Informed consent for specimens for Future Biomedical Research may also be obtained during screening and must be obtained prior to collection of all Future Biomedical Research specimens.

All patients who are consented will be registered in OnCore®, the UCSF Helen Diller Family Comprehensive Cancer Center Clinical Trial Management System (CTMS). The system is password protected and meets HIPAA requirements.

4 Treatment

Treatment will be administered on an outpatient basis.

4.1 Dose Escalation Schedule

The recommended starting dose of single agent epacadostat is 300 mg twice daily. The current study is designed to determine the MTD of epacadostat in combination with pembrolizumab and tavo-EP.

Table 4-1: Dose Escalation for epacadostat

Dose	N	Epacadostat(mg) (po BID) in 28 day cycles
-1	3	200 mg
0	3	300 mg
1	3	600 mg

Rationale for dose levels -1 to 1: The primary endpoint of the dose escalation safety run-in is to determine if epacadostat at 600 mg is a safe and tolerable dose in the combination of tavo-EP and pembrolizumab in patients with recurrent or metastatic squamous cell carcinoma of the head and neck with tumors.

The starting dose will be dose level 0. Dose level -1 may be selected if higher dosing cohorts are not tolerated.

Higher dose of epacadostat will be considered if no DLTs are seen at dose level 0. e.g. 300 mg bid.

4.2 Dose Expansion Schedule

Table 4-2: Dose Expansion Arms in both Stage 1 and 2

	Treatment Arms	N	Epacadostat	pembrolizumab	tavo-EP
Arm A	tavo-EP, pembrolizumab ad epacadostat	28*	MTD - as determine by dose escalation	200 mg via IV. Days 1 and 22 of each cycle for 6 weeks (42 days)	¼ tumor volume at concentration of 0.5 mg/mL[1] given intratumoral on Days 1, 5, 8 of each cycle for 6 weeks (42 days)
Arm B	tavo-EP and pembrolizumab	28			

*Patients in the dose escalation safety lead-in will have an opportunity to participate in Stage 1, Arm A per Investigator's discretion.

Rationale for cohort expansion: In the dose expansion cohorts, we will determine the tolerability of this combination, the recommended phase II dose (RP2D) and preliminary efficacy in 56 evaluable patients with recurrent or metastatic squamous cell carcinoma of the head and neck with tumors. Hence the cohort expansion warrants the confirmation of tolerability of this combination, was deemed safe will be pursued for further patients.

4.3 Dose Limiting Toxicity (DLT) and Maximum Tolerated Dose (MTD)

If DLT is encountered during the first cycle, the following rules (see table below) will be applied. If no DLT is encountered at a given dose level, escalation will be continued to the next higher dose level. If no DLT is found at the highest cohort, this cohort will be considered the recommended Stage 1 dose for epacadostat.

Table 4-3: Dose Escalation Decision Rules - DLT and MTD

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Escalate dose to next higher dose level
1 out of 3	Enter at least 3 more patients at this dose level If 0 of these 3 additional patients experience DLT (1 of 6), proceed to the next dose level If 1 or more of the 3 additional patients suffer DLT (2 of 6), then dose escalation is stopped and this dose is declared the maximal administered dose (highest dose administered) Determination of the MTD will continue at the next lowest dose cohort, at which an additional 3 patients will be added, for a total of 6 (unless that cohort already has 6 patients)

≥ 2 out of 3	Dose escalation will be stopped This dose level is declared the maximum administered dose The next lower cohort will be expanded to 6 patients If < 1 experience DLT, this dose is the maximal tolerated dose (MTD)
≤ 1 out of 6 at highest dose level below the maximum administered dose	This is generally the recommended Phase 2 dose At least 6 patients must be entered at the recommended Phase 2 dose

4.3.1 Dose Limiting Toxicity

Adverse Events and other symptoms will be graded according to the NCI Common Terminology Criteria for Adverse Events Version 4.03 (NCI, CTC web site http://ctep.info.nih.gov).

A DLT will be defined as any one of the following adverse events occurring during Cycle 1 when association to therapy that is part of this study is related or possibly related:

1. Hematologic dose-limiting toxicity

   - Grade 4 neutropenia lasting for ≥7 days in duration.
   - Febrile neutropenia of any grade
   - Grade 4 thrombocytopenia (≤25.0 x 10^9/L) lasting for ≥7 days in duration.
   - Grade 3 thrombocytopenia complicated by clinically significant bleeding and/or requiring platelet or blood transfusion

2. Non-hematologic dose-limiting toxicity

This will be defined as any Grade ≥3 non-hematologic toxicity, which is clinically meaningful and related with the specific **EXCEPTION** of:

- Any grade alopecia
- Grade 3 total hyperbilirubinemia if <35% is direct component
- Grade 3 transient ALT/AST elevation
- Grade 3 rash, nausea, vomiting or diarrhea for ≤ 3 days or is not properly managed with optimal supportive care
- Grade 3 lab abnormalities must be clinically significant, meaningful and dose related.

4.3.2 Dose Modifications and Management of Toxicity

Dose modifications are permitted in Cycle 1 only in the event of a DLT.

Dose modifications of epacadostat will be made per the dose escalation table.

1. If dose reduction of epacadostat is necessary:
    - The dose should be reduced stepwise based on the dose escalation table. The patient should be monitored for approximately 10 to 14 days at each dose level.

Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation. After cycle 2, patients who have benefit are allowed to request treatment interruptions for personal reasons up to three weeks. Longer treatment interruptions must be approved by the PI and the drug sponsor.

The following dose modification rules will be used with respect to potential toxicity. Toxicity will be assessed according to the NCI Common Terminology Criteria for Adverse Events Version 4.03 (CTCAE v4.03).

4.3.3 Treatment Modification – All Agents

Adverse events associated with treatment on study may be immune-related or not immune-related. Immune-related AEs (irAEs) may be predicted based on the nature of the compounds, their mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. Special attention should be paid to AEs that may be suggestive of potential irAEs. An irAE can occur shortly after the first dose or several months after the last dose of treatment. If an irAE is suspected, efforts should be made based on the investigator's clinical judgment to rule out neoplastic, infectious, metabolic, toxins, or other etiologic causes prior to labeling an AE as an irAE.

In some circumstances, it may be necessary to temporarily interrupt pembrolizumab, tavo-EP or epacadostat as a result of AEs that may have an unclear relationship to any individual study drug. If an interruption for an adverse event is necessary and the causative agent cannot be identified, all agents should be interrupted. Immune-related adverse events may also be attributable to epacadostat alone, pembrolizumab alone, tavo-EP, alone or the combination of two or three of these agents. If the event is clearly related to one of the agents, follow the instructions specific for that agent. If the event is related to more than one agent, follow the action taken instructions for each causative agent.

General supportive care recommendations to manage irAEs are detailed in *Table 4-4.* Additional treatment modification recommendations may be found in subsequent sections, in the pembrolizumab package insert, and in the investigator's brochures for epacadostat and tavo-EP.

Table 4-4: General Guidelines for Immune-Related Adverse Events

irAE Toxicity Grade	**Withhold/Discontinue Agent(s)**	**Action Taken With Respect to Agent(s)**	**Supportive Care**
Grade 1	No action.	Not applicable.	Provide symptomatic treatment.

Grade 2	May withhold agent per investigator's discretion.	Not applicable. Investigators discretion.	Consider systemic corticosteroids in addition to appropriate symptomatic treatment.
Grade 3	Withhold or discontinue agent(s). Discontinue if unable to reduce corticosteroid dose to < 10 mg/day of prednisone or equivalent within 6 weeks of toxicity.	Return to treatment if improves to Grade 1 or resolves within 6 weeks. If AE resolves within 4 weeks, subject may restart at the same dose and schedule for epacadostat. For an AE that does not resolve within 4 weeks, agent(s) should be reduced 1 dose level. If AE does not resolve within 6 weeks, study treatment with agent(s) should be discontinued or discussed with principal investigator.	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 1 and tapered over at least 4 weeks in most cases.
Grade 4	Discontinue agent(s).	Not applicable. Any exceptions require principal investigator approval.	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 1 and tapered over at least 4 weeks in most cases.

Any interruptions of > 2 weeks or for LFT abnormalities must be discussed with the principal investigator before resuming treatment. Treatment with epacadostat, pembrolizumab, and tavo-EP should be withheld for drug-related Grade 4 hematologic toxicities, non-hematological toxicity ≥ Grade 3 (including laboratory abnormalities), and severe or life-threatening AEs.

Discontinuation Rules and Procedures for Specific Immune-Related Adverse Events Associated with Epacadostat and Pembrolizumab

Supportive care measures for the management of adverse events with potential immunologic etiology that are, in the judgment of the investigator, at least possibly associated with pembrolizumab and/or epacadostat are outlined in **Table 4-5** below and **Table 4-6** for pembrolizumab infusion-related reactions. For AEs listed in **Table 4-5** *and* **Table 4-6**, follow the guidelines in **Table 4-5***, and* **Table 4-6**. For AEs not listed in **Table 4-5** *or* Table 4-6, follow the guidelines in **Table 4-4**. For each disorder listed in **Table 4-5**, and **Table 4-6** attempts should be made based in the investigator's clinical judgment to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care.

Table 4-5: Dose Modification Guidance for Epacadostat and Pembrolizumab

Adverse Event	CTCAE v4.03 Grade	Action Taken
Adrenal Insufficiency	2	Hold pembrolizumab and epacadostat until patient is clinically stable. Treat with corticosteroids. If toxicity worsens, then treat as Grade 3 or Grade 4. Pembrolizumab and epacadostat can be resumed once event stabilizes and after completion of steroid taper. Patient can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator or treating physician's clinical judgement. 3. Doses of prednisone are ≤10 mg/day or equivalent.
	3 or 4	Hold pembrolizumab and epacadostat until patient is clinically stable. Treat with corticosteroids. Pembrolizumab and epacadostat can be resumed once event stabilizes and after completion of steroid taper. Patient can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator or treating physician's clinical judgement. 3. Doses of prednisone are ≤10 mg/day or equivalent.

Adverse Event	CTCAE v4.03 Grade	Action Taken
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 pembrolizumab, 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 epacadostat and pembrolizumab, 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 and pembrolizumab at the same dose.
	3	Interrupt epacadostat and pembrolizumab. When diarrhea resolves to baseline, resume pembrolizumab and 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 diarrhea, consider further dose reduction of epacadostat, or discontinuation of pembrolizumab and epacadostat.
	4	Discontinue epacadostat and pembrolizumab
Pneumonitis	2	Interrupt epacadostat and pembrolizumab 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.

Adverse Event	CTCAE v4.03 Grade	Action Taken
	3 or 4	Permanently discontinue epacadostat and pembrolizumab. 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)	Newly onset TIDM or Grade 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. Once serum glucose is stabilized, pembrolizumab, tavo-EP and epacadostat should restart at the same dose if the episode is thought to be unrelated to treatment. If the episode is related, resume treatment with a one level dose reduction of epacadostat.
Hypophysitis	2	Hold pembrolizumab and epacadostat. 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.
	3 or 4	Discontinue epacadostat and pembrolizumab. Treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
Hyperthyroidism or hypothyroidism	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	Action Taken
	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. Once hyperthyroidism has resolved and steroids tapered, subject may resume epacadostat, pembrolizumab and tavo-EP or permanently discontinue at the discretion of the investigator.
Hepatic	2	Hold pembrolizumab and epacadostat. 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	Permanently discontinue pembrolizumab and epacadostat if related to these agents. 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. If unrelated to pembrolizumab, treatment with pembrolizumab and epacadostat may be resumed once steroids have been discontinued.
Myocarditis	2	Hold pembrolizumab and epacadostat until resolution to Grade 0. Monitor symptoms daily, hospitalize. Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy. Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]). If toxicity rapidly improves to Grade 0, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper. If toxicity does not rapidly improve, permanently discontinue pembrolizumab and epacadostat.

Adverse Event	CTCAE v4.03 Grade	Action Taken
	3 or 4	Permanently discontinue pembrolizumab and epacadostat if related to these agents. Monitor symptoms daily, hospitalize. Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy. Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).
Renal failure or nephritis	2	Treat with oral corticosteroids.
	3 or 4	Permanently discontinue pembrolizumab and epacadostat if related to these agents. 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. If unrelated to pembrolizumab, treatment with pembrolizumab and epacadostat may be resumed once steroids have been discontinued.
Any toxicity, if clinically significant and not manageable by supportive care	2 or 3	Interrupt epacadostat and pembrolizumab if toxicity is attributed to epacadostat and pembrolizumab. When toxicity resolves to ≤ Grade 1, resume pembrolizumab and epacadostat. For recurrent or persistent Grade 2 or 3 toxicity that is clinically significant and not manageable with supportive care, consider further dose reduction of epacadostat or epacadostat and pembrolizumab discontinuation.
Other AEs	4	In general, epacadostat and pembrolizumab should be discontinued. Treatment with epacadostat and pembrolizumab may only be restarted after consideration of the benefit versus the risk and the approval of the principal investigator.

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

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

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

Dose modification and toxicity management of infusion-reactions related to pembrolizumab

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in **Error! Reference source not found.**

Table 4-6: Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 **Mild reaction; infusion interruption not indicated; intervention not indicated**	**Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.**	**None**
Grade 2 **Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.**	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr. to 50	Participant may be pre-medicated 1.5h (± 30 minutes) prior to infusion of _____ with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). **Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).**

	mL/hr.). Otherwise dosing will be held until symptoms resolve and the participant should be pre-medicated for the next scheduled dose. Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment	
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: • Epinephrine** • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids • Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • Hospitalization may be indicated. • **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug treatment.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration**. For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov**		

Guidelines for Subjects Exhibiting Serotonin Syndrome

There is a rare chance that epacadostat could cause an increase in serotonin levels in the brain that might trigger Serotonin Syndrome when administered in combination with other serotonergic agents. This syndrome has been most closely associated with use of MAOIs, meperidine, linezolid, or methylene blue; all of these agents are prohibited during the study. Serotonin reuptake inhibitors (SSRIs) and serotonin/norepinephrine reuptake inhibitors (SNRIs) are permitted in the study. Serotonin syndrome usually manifests with autonomic changes, mental status changes, and neurological findings. Mild, moderate, and severe signs and symptoms of SS are summarized in table below and should be evaluated in the context of possible comorbid conditions as well. The following procedures will be implemented if participants exhibit the signs/symptoms of SS described in the following table:

- Immediately interrupt epacadostat or matching placebo administration. Administration of pembrolizumab may continue.
- Immediately interrupt any SSRI or SNRI administration.

Provide appropriate medical management of the participant until all signs/symptoms are resolved (e.g., IV fluids and/or sympathomimetic amines for hypotension, benzodiazepines for agitation, administration of 5-hydroxytryptamine antagonists such as cyproheptadine).

If participant chooses to remain in the study, restart treatment with epacadostat or matching placebo after the SSRI or SNRI has been discontinued, no sooner than 5 half-lives have elapsed for the specific SSRI or SNRI in question, and after resolution of signs/symptoms of SS. The SSRI or SNRI dosing MAY NOT be restarted.

If participant chooses to withdraw from the study, or must restart treatment with SSRI or SNRI, the participant 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.

Additionally, sites should contact the Incyte Clinical Director if Serotonin Syndrome is suspected.

Table 4-7: Sign and Symptoms of Serotonin Syndrome

4.3.4 Seriousness	**4.3.5** Autonomic signs	**4.3.6** Neurological signs	**4.3.7** Mental status	**4.3.8** Other
4.3.9 Mild	Afebrile or low-grade fever	Intermittent tremor	Restlessness	
	Tachycardia	Akathisia	Anxiety	
	Mydriasis	Myoclonus		
	Diaphoresis or shivering	Mild hyperreflexia		
4.3.10 Moderate	Increased Tachycardia	Hyperreflexia	Easily startled	Rhabdomyolysis
	Fever (up to 41 ^{0}C)	Inducible clonus	Increased confusion	Metabolic acidosis

	Diarrhea with hyperactive bowel sounds	Ocular clonus (slow continuous lateral eye movements)	Agitation and hypervigilance	Renal Failure
	Diaphoresis with normal skin color	Myoclonus		Disseminated intravascular coagulopathy (secondary to hyperthermia)
4.3.11 Severe	Temperature often more than 41 0C (Secondary to increased tone)	Increased muscle tone (lower limb > upper)	Delirium	As above
		Spontaneous clonus	Coma	
		Substantial myoclonus or hyperreflexia		

[1] Boyer EW, Shannon M. The serotonin syndrome. New Engl J Med 2005;352: 1112-1120.

Dose Modification versus Dose Interruption

Epacadostat, pembrolizumab and tavo-EP may be held for up to 6 weeks as clinically indicated or required due to treatment associated AEs but dose reductions are not permitted.

Dosing interruptions of all agents may be permitted in the case of medical/surgical events or logistical reasons not related to study therapy (eg, elective surgery, unrelated medical events, subject vacation, and/or holidays). Subjects should be placed back on study therapy within 6 weeks of the scheduled interruption. The reason for interruption should be documented in the subject's study record.

4.4 Duration of Treatment

During the treatment phase, patients will receive combination therapy for 12 months or until the development of unacceptable treatment associated toxicity or confirmed progression. After the initial 12 months of therapy, patients who remain on treatment will enter the follow-up phase for the next 24 months. Patients with disease progression during the follow-up phase will have access to 12 additional months of triplet therapy. Patients who are eligible for treatment on study but who have experienced regression of all previously accessible lesions may continue on pembrolizumab and epacadostat without tavo-EP.

4.4.1 Treatment After Disease Progression

Patients with disease progression by RECIST version 1.1 who are benefiting from treatment in the opinion of the principal investigator may continue on treatment for up to 12 months from the initiation (or re-initiation) of treatment on study.

4.5 Post-Treatment Follow-up

Patients will be followed for toxicity and radiographic imaging will be performed at 3 month intervals 1) until start of a new anti-cancer treatment, (2) until 30 days after documented

disease progression, (3) until death, or (4) until 36 months from the initiation of treatment on study, whichever comes first. Each subject will be followed for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

4.6 Clinical and Pharmacy Considerations

4.6.1 tavo-EP

4.6.1.1 Drug Availability, Handling, and Storage

Availability

Plasmid interleukin-12 (tavo-EP) is formulated in phosphate buffered saline (PBS) for direct intratumoral injection following by *in vivo* EP. GMP-grade tavo-EP is manufactured by VGXI USA and available batches will be supplied as 2.0 mL vials at a concentration of 0.5 mg/mL and fill volume of 1.7 mL.

Storage and handling

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

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

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

Unopened vials of tavo-EP must be stored at -20°C ±5°C. Once thawed, the plasmid solution will be drawn into a tuberculin syringe with a 25-gauge 5/8-inch needle. Only authorized investigators listed on the form FDA 1572 will administer the plasmid injection. Once thawed, the tavo-EP solution should be stored at 4ºC and used within 8 hours as supported by in-use stability testing. Refer to the tavo Pharmacy manual for details.

Accountability

The Investigational Pharmacist will manage drug accountability records.

Drug Ordering

A 3rd party vendor CRO, will be supplying the tavo-EP to the investigational site.

Packaging and Labeling of epacadostat, pembrolizumab, and tavo-EP

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

Clinical Supplies Disclosure

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

Returns and Reconciliation

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

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

4.6.1.2 Administration

Prior to plasmid injection, using sterile precautions, 1% lidocaine may be injected around the lesion to obtain local anesthesia. In addition, the patient may be given analgesics or anxiolytics as necessary prior to or during treatment. *tavo-EP:*pUMVC3-hIL-12-NGVL33 (tavo-EP) will be injected intratumorally to accessible lesions without exceeding 20 mL per day. After injecting the plasmid solution into the accessible tumor, an Immunopulse® applicator containing 6 stainless steel electrodes will be inserted into the tumor such that the electrode span the plasmid injection site. The applicator will be connected to the power supply and six pulses at a field strength (E+) of 1300 V/cm and pulse width of 100 µs at 1-second intervals will be administered to each previously injected tumor.

4.6.1.3 Treatment Parameters

Intratumoral tavo-may be administered at each odd cycle as long as the subject has at least one accessible lesion (AL) for treatment. An AL is defined as meeting the following criteria; (1) at least 0.3 cm x 0.3 cm in longest perpendicular diameters, (2) in a suitable location for application of electroporation. This includes visible or palpable sites in the oral cavity or oropharynx, palpable lymph nodes, and cutaneous lesions. Prior to initiation of a new treatment cycle of tavo-EP EP, the investigator will determine ALs for treatment during that cycle based on the most recent schedule tumor measurements. The same ALs must be treated on each day of the cycle (i.e. Days 1, 55, 8). Previously treated, previously identified lesions present at baseline that were left untreated and new lesions which appear during the course of the study that meet the definition of an AL may be treated as long as the maximum plasmid injection volume per patient per day does not exceed 20 mL. Tumors invading the carotid artery or at other sites that the investigator believes to be at high risk of life-threatening hemorrhage should not be injected.

4.6.1.4 Dose Holds

If no ALs are present at subsequent cycles, the subject may skip that cycle of tavo-EP and continue on the study calendar (**Table 3-1**). Treatment should also be held if the patient develops any sustained grade 3 or higher adverse event other than rash that is at least possibly attributed to tavo-EP in the opinion of the treating investigator. Tavo-EP may be resumed once the AE resolves to grade 1 or lower. Treatment should also be held for any intolerable rash or if holding treatment is in the best interests of the patient in the opinion of the treating investigator.

4.6.2 Epacadostat

4.6.2.1 Supply, Packaging, and Labeling

Epacadostat is available as 25, 100 and 300 mg tablets packaged in high-density polyethylene bottles.

4.6.2.2 Storage

Clinical supplies must be stored as described in the IB.

4.6.2.3 Administration

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

Subjects will begin treatment with epacadostat on cycle 1, day 1 of the study and will continue administration through the end of treatment. There is no priority to the order of administration of epacadostat, pembrolizumab, and tavo-EP when administered in combination; however, the dose of epacadostat should be taken as close to the regularly scheduled 12-hour dosing interval as possible.

4.6.3 Pembrolizumab

4.6.3.1 Supply, Packaging and Labeling

See manufacturer's guidelines as described in the package insert.

4.6.3.2 Storage

See manufacturer's guidelines as described in the package insert.

4.6.3.3 Administration

See manufacturer's guidelines as described in the package insert.

5 Safety

5.1 Safety Assessments

Clinical evaluations including laboratory and clinical safety assessments will be performed at 3-week intervals for patients who are actively receiving treatment on study. For patients in the follow-up portions of the study who are not actively receiving therapy, evaluations will be performed at 12-week intervals. Safety assessments are outlined in the Study Calendar (**Table 3-1**). Safety assessments include AEs (either reported by the patient or observed by the Investigator), concomitant medication use, performance status, vital signs, physical examination, and laboratory assessments. AEs will be graded and reported using CTCAE version 4 and reported descriptively.

5.2 Safety Stopping Rules

Clinical evaluations including laboratory and clinical safety assessments will be performed at 3-week intervals for patients who are actively receiving treatment on study. For patients in the follow-up portions of the study who are not actively receiving therapy, evaluations will be performed at 12-week intervals. Safety will be assessed during the study by documentation of adverse events (AEs), clinical laboratory tests, physical examination, vital sign measurements, and Eastern Cooperative Oncology Group (ECOG) performance status.

Lead-In Period and De-Escalation

1. If, at any time, 2 or more of the first 6 safety-evaluable patients experience grade 3 or higher treatment-associated adverse events within the first 30 days of initiation of treatment, then no further patients will be enrolled at the current dose level.

2. After 6 patients have been enrolled on study, enrollment will be halted for 30 days for completion of lead-in safety analysis. If 0-1 patients experience grade 3 or higher treatment-associated adverse events within the first 30 days of initiation of treatment, then additional patients may be enrolled at the current dose level.

3. If enrollment is halted at any time during the lead-in period due to treatment-associated adverse events, the UCSF DSMB will review all available safety data with the Principal Investigator. Based on this review, study discontinuation or reduction of the epacadostat dose may be recommended. No further patients will be enrolled on study without the approval of the DSMB. If the DSMB allows additional patients to enroll, the lead-in period will be repeated at the new dose level with a maximum of 6 additional patients enrolled prior to follow-up safety analysis. At the discretion of the DSMB, patients who are currently on study may continue treatment at the reduced dose level.

4. Patients who discontinue treatment on study within 30 days of initiation of therapy for reasons other than treatment-associated toxicity will be deemed inevaluable for safety and replaced for safety analysis.

Mid-Study Interim Safety Analysis

Enrollment will also be halted for 30 days for interim safety analyses after a total of 30 safety-evaluable patients have initiated treatment on study. Patients who discontinue treatment on study within 30 days of initiation of therapy for reasons other than treatment-associated toxicity will be deemed inevaluable for safety and replaced for safety analysis. The study will be discontinued under the following circumstance:

1. On-study occurrence of 3 or more Grade 4 (life threatening) serious adverse events (SAEs) or deaths, which are deemed at least possibly related to the study agent.

2. Based on the review of data the DSMB has serious concerns about the safety of patients on the study. In addition to stopping the study, the DSMB may recommend

that the epacadostat dose for all patients be de-escalated for all current and future patients, or cessation of further patient accrual.

Safety review at participating sites

During the dose escalation safety lead-in phase of the study, weekly calls will be scheduled to review the safety data at all sites. Once the lead-in phase is completed, calls with be scheduled monthly. All sites with any active patients on study will be expected to have at least one representative on these calls. One or more representatives of the UCSF DSMC will be invited to participate as well.

6 Efficacy Assessments

MRI, contrast-enhanced CT, or PET/CT imaging of the face, neck, chest, abdomen, and pelvis are required at screening and on day 1 of each odd-numbered cycle excluding cycle 1. Both clinical and radiographic measurements may be used. All superficial, clinically apparent lesions that cannot be adequately assessed radiographically (e. g. subcutaneous lesions) must be numbered and photographed with a metric ruler visible in each photograph. For photographed lesions with borders that are not clearly visible, investigators should trace the lesions' outline, making a solid line with a felt-tipped pen. Visible lesions should never be circled with a solid line but dashed or dotted lines may be used to distinguish these markings from the borders of otherwise invisible lesions. Tumor assessments will be made using RECIST version 1.1. IL-12 plasmid dosing may be based on the most recent tumor measurements and measurements need not be repeated immediately prior to each tavo-EP treatment.

6.1 Efficacy Assessments

Response to treatment in this study will be evaluated using the international criteria proposed by the RECIST Committee (Therasse et al. 2000a), modified in 2009 (Eisenhauer et al. 2009) and clarified for disease-specific adaptation (Schwartz et al. 2016). The primary efficacy endpoint, BORR, will be evaluated using RECIST v1.1 (**Section 6.1.1.1**).

6.1.1 Response Evaluation Criteria in Solid Tumors (RECIST) v1.1

Tumor response will be evaluated according to RECIST guidelines (Therasse et al. 2000b) using tumor imaging (see **Section 6.1.1.1** for tumor imaging details).

Assessment by RECIST v1.1 will be done at 12-week intervals as specified in **Table 3-1**. Lesions will be numbered identically for each visit as target and non-target, new lesions (see definitions in **Table 6-1**). Tumor assessments during the Core study (over 24 weeks) will be

done by independent central radiologic review[1] and integrated medical oncologist disease assessment based on RECIST v1.1 and investigator assessment of RECIST and iRECIST (will be throughout the study).

In support of RECIST v1.1, when more than one accessible and measurable tumor is present at baseline, all lesions (those with the longest diameter(s)/ organ that are measurable in the physicians' discretion) up to 2 cutaneous lesions should be identified as measurable representative Target Lesions. A target lesion may be a treated or untreated lesion.
An 'accessible lesion' is defined as a cutaneous or subcutaneous lesion that can be reached from the surface with the electroporation needle array (with depth of up to 1.5 cm from the surface). Refer to section 5.1.1.3.

Each patient will be assigned a response category (**Table 6-1**

Table 6-1 Response Evaluation Criteria in Solid Tumors v1.1): complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD).

Per RECIST 1.1, partial response (PR) or complete response (CR) should be confirmed by a repeat tumor imaging assessment not less than 4 weeks from the date the response was first documented. The tumor imaging for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan (i.e. 12 weeks later), whichever is clinically indicated.

[1] In accordance to FDA "Clinical Trial Imaging Endpoint Process Standards Guidance for Industry" (Version 1 March 2015);
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm268555.pdf

Table 6-1 Response Evaluation Criteria in Solid Tumors v1.1

RECIST v1.1 Response Criteria	Target Lesions	Non-Target Lesions
Complete Response (CR)[2]	Disappearance of all target lesions, determined by two separate observations conducted not less than 4 weeks apart. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (the sum may not be "0" if there are target nodes). There can be no appearance of new lesions.	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
Partial Response	At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. There can be no appearance of new lesions.	Non-target lesions must be non-PD.
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.	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

[2] Patients will meet the primary endpoint (BORR) if they attain a confirmed CR or PR over the 24 weeks with the combination treatment with a 4-week confirmatory scan per RECIST v1.1.

Progressive Disease (PD)	At least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥5 mm, or the appearance of one or more new lesions.	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

6.1.1.1 Evaluation of Best Overall Response with RECIST v1.1

The best overall response (BOR) is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria (**Table 6-2**).

Table 6-2: Overall Response Definitions using RECIST v1.1

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires
CR	CR	No	CR	Normalization of tumor markers, tumor nodes <10 mm
CR	Non-CR/ Non-PD	No	PR	
CR	Not all evaluated	No	PR	
PR	Non-PD / No all evaluated	No	PR	
SD	Non-PD	No	SD	Documented at least once ≥4 weeks from baseline
Not all evaluated	Non-PD	No	NE	
PD	Any	Any	PD	

Any	PD*	Any	PD	
Any	Any	Yes	PD	

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression Source: (Seymour et al. 2017)

Other definitions

- Progression free survival (PFS) – PFS is defined as the time, in months, from the first dosing date until the date of disease progression (i.e., the date of the tumor imaging) or death from any cause. RECIST v1.1 will be used to determine the dates of progression as this methodology is accepted by regulatory authorities. In addition, final determination of radiologic progression will be based on the central imaging vendor assessment of progression, rather than site study team assessment. Determination of radiologic progression as determined by central imaging vendor (verification of PD) will be communicated to the site study team.

7 Statistical Plan

7.1 Sample Size Justification

Dose Expansion Phase, Stage 1: We expect to enroll 30 patients in both arms (15 patients in Arm A and 15 patients in Arm B). We will allow patients who were enrolled in the dose escalation safety lead-in to enroll in Arm A of Stage 1, depending on the final dose.

Dose Expansion Phase, Stage 2: Depending on the results of the clinical data in Stage 1, Stage 2 will enroll up to an additional 26 patients accordingly:

If there are at least ≥ 3 responses in 15 patients, in either Arms A or B, up to an additional 26 patients (13 patients in Arm A and 13 patients in Arm B) will be enrolled in the respective treatment arms.

The above Simon 2-stage sample sizes were based on the following assumptions: the objective response rate for pembrolizumab is approximately 15%[3] and we suggest that a 20% absolute improvement in this response rate would be clinically meaningful. We propose to test the hypothesis that the objective response rate for the combination of tavo-EP with pembrolizumab and epacadostat is 35% versus the null hypothesis that it is similar to the response rate for pembrolizumab monotherapy, 15%. The statistical power calculations are based on the Simon Two-Stage Optimal Design[11] with a Type I error rate of 0.05 and power of 80%.

Efficacy Assessment:

The objective response rate for pembrolizumab is approximately 15%[3] and we suggest that a 20% absolute improvement in this response rate would be clinically meaningful. We propose to test the hypothesis that the objective response rate for the combination of tavo-EP with pembrolizumab and epacadostat is 35% versus the null hypothesis that it is similar

to the response rate for pembrolizumab monotherapy, 15%. The following statistical power calculations are based on the Simon Two-Stage Optimal Design[11] with a Type I error rate of 0.05 and power of 80%.

7.2 Analysis Populations

The analysis population is defined as All Treated Subjects, defined as all enrolled subjects who received at least one dose of study treatment. Efficacy and safety analyses will be completed in the All Treated Subjects population.

7.3 Primary Efficacy Analysis

The primary efficacy analysis will be conducted on All Treated Subjects, by treatment arm and dose levels as appropriate, and overall. The primary endpoint of BORR will be calculated and applied in the proceeding of Simon two-stage design, however, no formal statistical testing will be conducted between dose levels or between treatment arms as the sample size is not powered adequately for the testing, and comparisons will be made in a qualitative fashion.

Patients' best overall response will be summarized by the number and percentage of subjects who achieved a CR, PR, SD and PD. BORR is calculated as the percentage of patients who achieved a CR or PR relative to the total size of the All Treated Subjects population. The 95% confidence interval of BORR will be calculated by the Clopper-Pearson (exact binomial) method.

The primary endpoint of safety will be performed for all patients having received at least one dose of study drug. The study will use the NCI CTCAE v4.0.

7.4 Secondary/ Exploratory Efficacy Analysis

All secondary and exploratory efficacy analyses will be conducted on All Treated Subjects, by treatment arm and dose levels as appropriate, and overall.

The secondary endpoints of PFS and OS will be analyzed and plotted using the Kaplan-Meier method, estimates of the median will be provided and the 95% CI of median will be calculated by the Brookmeyer and Crowley method.

Time to response is defined as the number of days from the date of enrollment to the date of the first documented response of CR or PR. Time to response will be summarized by descriptive statistics including mean, median, and standard deviation, minimum and maximum.

Disease control rate (DCR) is defined as the percentage of patients who achieved a best overall response of CR, PR or SD. Clinical benefit rate (CBR) is defined as the percentage of patients who achieved a best overall response of CR, PR and SD with a duration of at least 6 months or longer. DCR and CBR will be analyzed using the method similar to BORR.

Duration of response (DOR) will be calculated for patients who achieved a best overall response of CR or PR, and calculated as the number of days from the date when CR or PR is first met to the date of progression or death. Patients who do not have a documented progression or death will be censored on the last date of tumor assessment. The number and percentage of patients whose DOR is longer than certain milestone times (such as 6 months,

9 months and 12 months) will be quantified. If the number of responders is sufficient, DOR may also be analyzed using the Kaplan-Meier method, with the median DOR and 95% CI calculated similar to PFS and OS analysis.

7.5 Exploratory Analysis

The plan for the exploratory / translational endpoint is described in **Appendix 4**. Correlative analyses between exploratory/translational endpoint and clinical endpoints may also be conducted if warranted.

7.6 Safety Analysis

Safety analyses will be conducted on All Treated Subjects, by treatment arm and dose levels as appropriate, and overall. Safety analyses will be based on adverse events, clinical laboratory tests, physical examination, and vital sign measurements. All adverse event will be graded using CTCAE version 4 or later. Safety analyses will be summarized using descriptive statistics. Continuous measurements will be summarized using n (number of subjects with the measured quantity), mean, and standard deviation, median, minimum and maximum. Categorical measurement will be summarized by frequencies and percentages.

8 Restricted Medications

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 routine monitoring.

	Epacadostat Dose
Stable Baseline INR	**≤ 300mg BID**
INR ≤ 2.5	Close INR monitoring
INR > 2.5	Close INR monitoring

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

Prohibited Medications/Treatment

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

- Any investigational medication other than pembrolizumab, epacadostat, and tavo-EP.
- Use of any anticancer medications, including chemotherapy or biologic therapy other than the study medications.

- 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.)
- Radiation therapy

  Note: In the presence of a mixed response (some lesions improving or stable and other lesions progressing), radiation therapy to a symptomatic solitary lesion or to the brain is allowed.
- Administration of a live attenuated vaccine within 30 days before the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.
- Use of any MAOI or drug associated with significant MAOI activity agents is prohibited from 21 days prior to Day 1 through 2 weeks after the final dose of epacadostat has been administered
- Use of any immunological-based treatment for any reason from screening through follow-up visit is prohibited.

  Note: Completed adjuvant therapy (eg, vaccines) with principal investigator 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 is allowed for short term sedation for biopsies.

Subjects may receive other medications that the investigator deems to be medically necessary.

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

9 Discontinuation of Therapy

The Investigator will withdraw a patient whenever continued participation is no longer in the patient's best interests. Reasons for withdrawing a patient include, but are not limited to, disease progression, the occurrence of an adverse event or a concurrent illness, a patient's

request to end participation, a patient's non-compliance or simply significant uncertainty on the part of the Investigator that continued participation is prudent. There may also be administrative reasons to terminate participation, such as concern about a patient's compliance with the prescribed treatment regimen.

9.1 Birth Control, Pregnancy and Paternity

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

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

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined above. Reporting of Pregnancy and Lactation to the DSMC is required. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

9.2 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the UCSF Data Safety Monitoring Committee (DSMC) without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the DSMC. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the DSMC and followed as described above.

Please note, the investigator will notify Incyte within 24 hours of investigator awareness.

9.3 Use in Nursing Women

It is unknown whether the study agents are excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

10 Correlative Studies

Tumor Biopsy:
The clinical investigator and study pathologist have the responsibility for submitting representative diagnostic material for banking. Please refer to the OncoSec Laboratory manual for detailed instructions regarding these assessments. Patients will have a research biopsy taken from at least one tumor site prior to the initiation of treatment. An additional biopsy should be taken on cycle 2 day 1(+/- 3 days) at progression/end of treatment, and additional biopsies may be performed if clinically indicated.

Biopsy Types
Punch, core, incisional, and excisional biopsy specimens are permitted and should be obtained using standard institutional practices. Tumor biopsy may be formalin fixed and paraffin-embedded or frozen at -80C. If core biopsies are used, 3-4 cores should be taken as feasible, but any attempt to acquire at least one specimen will meet protocol requirements. Fine needle aspiration biopsies are not acceptable. Biopsy requirements may be waived by the PI if biopsies pose an excess risk to the patient.

Blood Immune Response Collection:
Patients will have blood drawn for research as outlined in the *Study Calendar*. Blood for Immune response monitoring will be collected as follow: 40 ml of blood. Specimen distribution and required tubes will be specified in the laboratory manual.

Correlative Analyses:

Correlative analyses include but are not limited to:

- Analysis of paired biopsy specimens for changes in inflammatory gene expression (Nanostring), relative proportion of effector versus regulatory T cells (mIHC), evaluation of elaboration of inflammatory cytokines, T-cell repertoires, clonality, and other hallmarks of immune activation.
- Analysis of circulating T-cell populations for changes in the frequency and effector function of immune cells including short-lived effector cells and memory T cells.
- Analysis of pre- and post-treatment cytokine expression, T-cell repertoire, clonality
- Analysis of functional immune responses using Elispot and other assays.
- Additional assessments that could assist in the understanding of the immune response to cancer at the discretion of the principal investigator

10.1 Future Biomedical Research

Future Biomedical Research on blood and leftover tumor biopsy specimens will be performed on collected samples during this clinical trial. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma) and/or

the measurement of other analytes. This research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main biomarker correlative objectives). The objective is to explore and identify biomarkers that inform scientific understanding of this therapeutic treatment and tumor biology responses to combination therapy. Such studies will be conducted with appropriate statistical considerations and evaluation of results.

11 Reporting and Documentation of Results

11.1 Evaluation of Efficacy (or Activity)

11.1.1 Antitumor Effect – Solid Tumors

Response and progression in this study will be evaluated using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [JNCI 92(3):205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v1.1 criteria.

11.1.1.1 Definitions

Evaluable for toxicity

All patients will be evaluable for toxicity from the time of their first treatment with epacadostat, pembrolizumab, or tavo-EP.

Evaluable for objective response

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

11.1.1.2 Disease Parameters

Measurable disease

Measurable disease is defined as lesions (or tumors) that can be accurately measured in at least one dimension (longest diameter to be recorded) with a minimum size of 10mm by CT scan (irrespective of scanner type), 10mm caliper measurement by clinical exam (when superficial), and/or 20mm by chest X-ray (if clearly defined and surrounded by aerated lung).

All tumor measurements will be recorded in millimeters or decimal fractions of centimeters. Previously irradiated lesions are considered non-measurable except in cases of documented progression of the lesion since the completion of radiation therapy.It is recommended that previously irradiated lesions that would otherwise be considered measurable be followed closely by investigators by comments, measurements and photographs if applicable for retrospective review.

Target lesions

All measurable lesions up to a maximum of 5 lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions will be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will

be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Non-target lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. It is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. "multiple enlarged pelvic lymph nodes" or "multiple liver metastases"). Bone lesions may be measureable if ≥ 1 cm on MRI. Measurements of these lesions are not required, but the presence or absence of each will be noted throughout follow-up. It is recommended that bone lesions be followed closely by investigators with comments and measurements whenever possible for retrospective review.

Non-measurable disease

Non-measurable disease is all other lesions (or sites of disease), including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm using spiral CT scan). Leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques are all non-measurable.

11.1.1.3 Methods for Evaluation of Measurable Disease

All measurements will be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations will be performed as closely as possible to the beginning of treatment and never more than 28 days before the beginning of the treatment.

The same method of assessment and the same technique will be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Conventional CT (or PET-CT)

These techniques 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. If measurable disease is noted in other areas of the body, CT imaging of those areas should be performed as well. Whole-body PET-CT is the preferred imaging technique whenever possible.

11.1.1.4 Response Criteria

Evaluation of Target Lesions

Complete Response (CR)

Disappearance of all target lesions, determined by two separate observations conducted not less than 4 weeks apart. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (the sum may not be "0" if there are target nodes). There can be no appearance of new lesions.

Partial Response (PR)

At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. There can be no appearance of new lesions

Progressive Disease (PD)

At least a 20% increase in the sum of the SLD of target lesions, taking as reference the smallest sum SLD recorded since the treatment started and minimum 5 mm increase over the nadir, 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 Non-Target Lesions

Complete Response (CR)

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

Incomplete Response/Stable Disease (SD)

Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD)

Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

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 progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Table 10 Response Criteria

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires
CR	CR	No	CR	≥4 weeks confirmation
CR	Non-CR/ Non-PD	No	PR	≥4 weeks confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	documented at least once ≥4 weeks from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

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

Evaluation of Safety

Analyses will be performed for all patients having received at least one dose of epacadostat, pembrolizumab, or tavo-EP. The study will use the CTCAE v4.0 for reporting of adverse events and modified criteria for adverse events, see Section 5. Safety will be assessed during the study by documentation of adverse events (AEs), clinical laboratory tests, physical examination, vital sign measurements, and Eastern Cooperative Oncology Group (ECOG) performance status.

For multicenter studies, the Principal Investigator at the UCSF Coordinating Center will hold the role of Study Chair. The Study Chair is responsible for the overall conduct of the study and for monitoring its safety and progress at all participating sites.

11.3 Evaluating Adverse Events

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

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

Table 11-1: Evaluating Adverse Events

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

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of investigational product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer;** (that is not a condition of the study) **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	

Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Investigational product to be discontinued?	
Relationship to test drug	Did the Investigational product cause the adverse event? The determination of the likelihood that the Investigational product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the Investigational product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Investigational product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Investigational product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Investigational product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Investigational product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was the Investigational product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Investigational product; or (3) the trial is a single-dose drug trial); or (4) Investigational product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Investigational product in this study?

		If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Investigational product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE INVESTIGATIONAL PRODUCT, OR IF REEXPOSURE TO THE INVESTIGATIONAL PRODUCTPOSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Investigational product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following		**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of anInvestigational product relationship).**
Yes, there is a reasonable possibility of Investigational product relationship.		There is evidence of exposure to the Investigational product. The temporal sequence of the AE onset relative to the administration of the Investigational product is reasonable. The AE is more likely explained by the Investigational product than by another cause.
No, there is not a reasonable possibility Investigational product relationship		Subject did not receive the Investigational product OR temporal sequence of the AE onset relative to administration of the Investigational product is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)

11.3.1 Definitions of Adverse Events

11.3.1.1 Adverse Event

An adverse event (also known as an adverse experience) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. More specifically, an adverse event (can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An adverse event can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

11.3.1.2 Adverse reaction

An adverse reaction is defined as any adverse event caused by the use of a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

11.3.1.3 Suspected

A suspected adverse reaction is defined as any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" indicates that there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

11.3.1.4 Unexpected

An adverse event or suspected adverse reaction is considered *unexpected* if it is not listed in the investigator brochure or package insert(s), or is not listed at the specificity or severity that has been observed, or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

"Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Adverse events that would be anticipated to occur as part of the disease process are considered *unexpected* for the purposes of reporting because they would not be listed in the investigator brochure. For example, a certain number of non-acute deaths in a cancer trial would be anticipated as an outcome of the underlying disease, but such deaths would generally not be listed as a suspected adverse reaction in the investigator brochure.

Some adverse events are listed in the Investigator Brochure as occurring with the same class of drugs, or as anticipated from the pharmacological properties of the drug, even though they have not been observed with the drug under investigation. Such events would be considered *unexpected* until they have been observed with the drug under investigation. For example, although angioedema is anticipated to occur in some patients exposed to drugs in the ACE inhibitor class and angioedema would be described in the investigator brochure as a class effect, the first case of angioedema observed with the drug under investigation should be considered *unexpected* for reporting purposes.

11.3.1.5 Serious

An adverse event or suspected adverse reaction is considered *serious* if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life function
- Congenital anomaly/birth defect

Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

11.3.1.6 Life-threatening

An adverse event or suspected adverse reaction is considered *life-threatening* if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

11.4 Recording of an Adverse Event

All grade 3 and above adverse events will be entered into OnCore®, whether or not the event is believed to be associated with use of epacadostat, pembrolizumab, or tavo-EP. Data about these events and their severity will be recorded using the NCI CTCAE v4.0.

The Investigator will assign attribution of the possible association of the event with use of the investigational drug, and this information will be entered into OnCore® using the classification system listed below:

Relationship	Attribution	Description
Unrelated to investigational drug/intervention	Unrelated	The AE *is clearly NOT related* to the intervention
	Unlikely	The AE *is doubtfully related* to the intervention
Related to investigational drug/intervention	Possible	The AE *may be related* to the intervention
	Probable	The AE *is likely related* to the intervention
	Definite	The AE *is clearly related* to the intervention

Signs or symptoms reported as adverse events will be graded and recorded by the Investigator according to the CTCAE. When specific adverse events are not listed in the CTCAE they will be graded by the Investigator as *none*, *mild*, *moderate* or *severe* according to the following grades and definitions:

Grade 0 No AE (or within normal limits)

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Grade 2 Moderate; minimal, local, or noninvasive intervention (e.g., packing, cautery) indicated; limiting age-appropriate instrumental activities of daily living (ADL)

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL

Grade 4: Life-threatening consequences; urgent intervention indicated

Grade 5: Death related to AE

11.5 Follow-up of Adverse Events

All adverse events will be followed with appropriate medical management until resolved. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. For selected adverse events for which administration of the investigational drug was stopped, a re-challenge of the subject with the investigational drug may be conducted if considered both safe and ethical by the Investigator.

11.6 Adverse Events Monitoring

All adverse events, whether or not unexpected, and whether or not considered to be associated with the use of epacadostat, pembrolizumab, or tavo-EP, will be entered into OnCore®, as noted above.

The Investigator will assess all adverse events and determine reportability requirements to the UCSF Data and Safety Monitoring Committee (DSMC) and UCSF's Institutional Review Board, the Committee on Human Research (CHR); and, when the study is conducted under an Investigational New Drug Application (IND), to the Food and Drug Administration (FDA) if it meets the FDA reporting criteria.

All adverse events entered into OnCore® will be reviewed by the Helen Diller Family Comprehensive Cancer Center Site Committee on a weekly basis. The Site Committee will review and discuss at each weekly meeting the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of epacadostat, pembrolizumab, or tavo-EP.

All grade(s) 3-5 adverse events entered into OnCore® will be reviewed on a monthly basis at the Site Committee meetings. The Site Committee will review and discuss the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of epacadostat, pembrolizumab, or tavo-EP.

In addition, all suspected adverse reactions considered "serious" entered into OnCore®, will be reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings, which take place every six weeks.

For a detailed description of the Data and Safety Monitoring Plan for a Multicenter Phase 2or 3 Institutional Study at the Helen Diller Comprehensive Cancer Center please refer to **Appendix 2 Data and Safety Monitoring Plan for a Multicenter Institutional Study (For Lead-In Phase)** and **Appendix 3 Data and Safety Monitoring Plan for a Multicenter Study (Phase II or III study).**

11.7 Expedited Reporting

Reporting to the Data and Safety Monitoring Committee

If a death occurs during the treatment phase of the study or within 30 days after the last administration of epacadostat, pembrolizumab, or tavo-EP and it is determined to be related either to the epacadostat, pembrolizumab, or tavo-EP or to a study procedure, the Investigator or his/her designee must notify the DSMC Chair (or qualified alternate) within 1 business day of knowledge of the event. The contact may be by phone or e-mail.

Reporting to UCSF Committee on Human Research (Institutional Review Board)

The Principal Investigator must report events meeting the UCSF CHR definition of "Unanticipated Problem" (UP) within 10 business days of his/her awareness of the event.

Expedited Reporting to the Food and Drug Administration

If the study is being conducted under an IND, the Sponsor-Investigator is responsible for determining whether or not the suspected adverse reaction meets the criteria for expedited reporting in accordance with Federal Regulations (21 CFR §312.32).

The Investigator must report in an IND safety report any suspected adverse reaction that is both serious and unexpected. The Sponsor-Investigator needs to ensure that the event meets all three definitions:

- Suspected adverse reaction
- Unexpected
- Serious

If the adverse event does not meet all three of the definitions, it should not be submitted as an expedited IND safety report.

The timeline for submitting an IND safety report to FDA is no later than **15 calendar days** after the Investigator determines that the suspected adverse reaction qualifies for reporting (21 CFR 312.32(c)(1)).

Any unexpected fatal or life-threatening suspected adverse reaction will be reported to FDA no later than **7 calendar days** after the Investigator's initial receipt of the information (21 CFR 312.32(c)(2)).

Any relevant additional information that pertains to a previously submitted IND safety report will be submitted to FDA as a Follow-up IND Safety Report without delay, as soon as the information is available (21 CFR 312.32(d)(2)).

Reporting to Incyte, Merck and OncoSec:

All SAEs, including pregnancy and lactation exposure cases, must be reported to Incyteand OncoSec within 24 hours. For secondary institutions, they will notify our site within 24hour of the SAE and we will notify the appropriate sponsor contacts within 24 hours of our awareness of the event.

- Submit the completed SAE Report Form to:
    - Incyte/Telerx via e-mail [redacted] or fax ([redacted] within 24 hours of awareness that the SAE has occurred.
    - Also submit these forms to OncoSec via email [redacted]. within 24 hours of awareness that the SAE has occurred

- Transmit one e-mail or fax per SAE Report Form. Send each SAE Report Form separately, with a separate SAE Notification Cover Sheet (e.g., transmit two SAE reports as two separate e-mails/faxes, with two cover sheets)
- Complete the SAE Report Form in English.
- If hand-written, use black ink and BLOCK PRINT, and make sure that it is legible.
- Avoid the use of abbreviations on the report form.
- Tick all applicable boxes on the SAE Report Form.
- Rather than leaving a field blank, use 'N/A' (not applicable), 'ND' (not done), or 'None'.
- Ensure that the information provided on the SAE Report Form is consistent with the data recorded in the Case Report Form (CRF)/electronic Case Report Form (eCRF) and the source data.
- Do not provide medical records (e.g., discharge summary, test results) unless specifically requested by Incyte or OncoSec; instead, record the information that is relevant to the SAE on the SAE Report Form.
- Provide clinically significant follow-up information regarding SAEs to Incyte/Telerx and OncoSec within 24 hours of becoming aware of the information, via the same process as for the initial report.
- If you amend the original SAE Report Form, annotate all corrections or additions with the date and your initials. Strike through (with a single line) any information that no longer applies. Otherwise, complete a new SAE Report Form with the new or updated information.
- When providing follow-up information, indicate whether the information should be added to previously reported information or if the information should replace previously reported information. For example, when different medical terms are reported in Section 8 on the initial and follow-up reports, please indicate whether the SAE term(s) on the follow-up report is in addition to or replaces the term(s) on the initial report form. If the term is being replaced, strike through (with a single line) the SAE term that no longer applies and include the date and your initials.
- If follow-up information is provided on a new SAE Report Form and fields are left blank, it will be assumed by Incyte/Telerx and OncoSec that there is no change in the information from the previous report form.
- Where an SAE is followed by reports of recurrent episodes, complications, or progression of the initial SAE, all such reports must be submitted as follow-up to the original episode.
- If a new SAE that occurs at a different time interval is considered completely non-associated to a previously reported SAE, complete and submit a new SAE Report Form as an initial report.

Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements
3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects
4. Plans to modify or discontinue the development of epacadostat, pembrolizumab, or tavo-EP

12 Study Management

12.1 Pre-study Documentation

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

Before initiating this trial, the Investigator will have written and dated approval from the Institutional Review Board for the protocol, written informed consent form, subject recruitment materials, and any other written information to be provided to subjects before any protocol related procedures are performed on any subjects.

The clinical investigation will not begin until either FDA has determined that the study under the Investigational Drug Application (IND) is allowed to proceed or the Investigator has received a letter from FDA stating that the study is exempt from IND requirements.

The Investigator must comply with the applicable regulations in Title 21 of the Code of Federal Regulations (21 CFR §50, §54, and §312), GCP/ICH guidelines, and all applicable regulatory requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

12.2 Institutional Review Board Approval

The protocol, the proposed informed consent form, and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the UCSF CHR (UCSF Institutional Review Board). Prior to obtaining CHR approval, the protocol must be approved by the Helen Diller Family Comprehensive Cancer Center Site Committee and by the Protocol Review Committee (PRC). The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

12.3 Informed Consent

All participants must be provided a consent form describing the study with sufficient information for each participant to make an informed decision regarding their participation. Participants must sign the CHR-approved informed consent form prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

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

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

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

that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

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

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

12.4 Changes in the Protocol

Once the protocol has been approved by the UCSF IRB, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the Investigator and approved by PRC and the IRB prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to patients, an amendment may be implemented prior to IRB approval. In this circumstance, however, the Investigator must then notify the IRB in writing within five (5) working days after implementation. The Study Chair and the UCSF study team will be responsible for updating any participating sites.

12.5 Handling and Documentation of Clinical Supplies

The UCSF Principal Investigator and each participating site will maintain complete records showing the receipt, dispensation, return, or other disposition of all investigational drugs. The date, quantity and batch or code number of the drug, and the identification of patients to whom epacadostat, pembrolizumab, or tavo-EP has been dispensed by patient number and initials will be included. The sponsor-investigator will maintain written records of any disposition of epacadostat, pembrolizumab, and tavo-EP.

The Principal Investigator shall not make the investigational drug available to any individuals other than to qualified study patients. Furthermore, the Principal Investigator will not allow the investigational drug to be used in any manner other than that specified in this protocol.

12.6 Case Report Forms (CRFs)

The Principal Investigator and/or his/her designee, will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into OnCore® via standardized CRFs in accordance with the CTMS study calendar, using single data entry with a secure access account. The Clinical Research Coordinator (CRC) will complete the CRFs as soon as possible upon completion of the study visit; the Investigator will review and approve the completed CRFs.

The information collected on CRFs shall be identical to that appearing in original source documents. Source documents will be found in the patient's medical records maintained by UCSF personnel. All source documentation should be kept in separate research folders for each patient.

In accordance with federal regulations, the Investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs. The PI will approve all completed CRFs to attest that the information contained on the CRFs is true and accurate.

All source documentation and CTMS data will be available for review/monitoring by the UCSF DSMC and regulatory agencies.

The Principal Investigator will be responsible for ensuring the accurate capture of study data. At study completion, when the CRFs have been declared to be complete and accurate, the database will be locked. Any changes to the data entered into the CRFs after that time can only be made by joint written agreement among the Study Chair, the Trial Statistician, and the Protocol Project Manager.

Each participating site will complete study specific CRFs for safety monitoring and data analysis. Each site will enter the study data into OnCore® via standardized CRFs in accordance with the CTMS study calendar, using single data entry with a secure access account. The participating site's Clinical Research Coordinator (CRC) will complete the CRFs; the Investigator will review and approve the completed CRFs – this process must be completed within 3 business days of the visit. Study data from the participating site will be reported and reviewed in aggregate with data from patients enrolled at the coordinating center, UCSF. All source documentation and CTMS data will be available for review/monitoring as needed.

12.7 Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center DSMC will be the monitoring entity for this study. The UCSF DSMC will monitor the study in accordance with the NCI-approved Data and Safety Monitoring Plan (DSMP). The DSMC will routinely review all adverse events and suspected adverse reactions considered "serious". The DSMC will audit study-related activities to ensure that the study is conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). Significant results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as applicable. See **Appendix 2 Data and Safety Monitoring Plan for a Multicenter Institutional Study (For Lead-In Phase)** and **Appendix 3 Data and Safety Monitoring Plan for a Multicenter Study (Phase II or III study)**, for additional information.

12.8 Multicenter communication

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center for Phase II studies will also coordinate, at minimum, monthly conference calls with the participating sites at the completion of each cohort or more frequently as needed to discuss risk assessment. The following issues will be discussed as appropriate:

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

12.9 Record Keeping and Record Retention

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

The Principal Investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each

individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

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

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

In accordance with FDA regulations, the investigator shall retain records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

12.10 Coordinating Center Documentation of Distribution

It is the responsibility of the Study Chair to maintain adequate files documenting the distribution of study documents as well as their receipt (when possible). The HDFCCC recommends that the Study Chair maintain a correspondence file and log for each segment of distribution (e.g., FDA, drug manufacturer, participating sites, etc.).

Correspondence file: should contain copies (paper or electronic) of all protocol versions, cover letters, amendment outlines (summary of changes), etc., along with distribution documentation and (when available) documentation of receipt.

Correspondence log: should be a brief list of all documents distributed including the date sent, recipient(s), and (if available) a tracking number and date received.

At a minimum, the Study Chair must keep documentation of when and to whom the protocol, its updates and safety information are distributed.

12.11 Regulatory Documentation

Prior to implementing this protocol at UCSF HDFCCC, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the UCSF Committee on Human Research (CHR). Prior to implementing this protocol at the participating sites, approval for the UCSF CHR approved protocol must be obtained from the participating site's IRB.

The following documents must be provided to UCSF HDFCCC before the participating site can be initiated and begin enrolling participants:

- Participating Site IRB approval(s) for the protocol, appendices, informed consent form and HIPAA authorization
- Participating Site IRB approved consent form
- Participating Site IRB membership list
- Participating Site IRB's Federal Wide Assurance number and OHRP Registration number
- Curriculum vitae and medical license for each investigator and consenting professional

- Documentation of Human Subject Research Certification training for investigators and key staff members at the Participating Site
- Participating site laboratory certifications and normal ranges.

Upon receipt of the required documents, UCSF HDFCCC will formally contact the site and grant permission to proceed with enrollment.

13 Protection of Human Subjects

13.1 Protection from Unnecessary Harm

Each clinical site is responsible for protecting all subjects involved in human experimentation. This is accomplished through the CHR mechanism and the process of informed consent. The CHR reviews all proposed studies involving human experimentation and ensures that the subject's rights and welfare are protected and that the potential benefits and/or the importance of the knowledge to be gained outweigh the risks to the individual. The CHR also reviews the informed consent document associated with each study in order to ensure that the consent document accurately and clearly communicates the nature of the research to be done and its associated risks and benefits.

13.2 Protection of Privacy

Patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be asked to sign the HIPAA form and informed consent documents. The original signed document will become part of the patient's medical records, and each patient will receive a copy of the signed document. The use and disclosure of protected health information will be limited to the individuals described in the informed consent document.

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Appendices

Appendix 1 Performance Status Criteria

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

Appendix 2 Data and Safety Monitoring Plan for a Multicenter Institutional Study (For Lead-In Phase)

1. Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all HDFCCC institutional clinical studies. A summary of DSMC activities for this study includes:

- Review of patient data in each cohort.
- Review of serious adverse events.
- Approval of dose escalation by DSMC Chair or Vice Chair.
- Real time monitoring (depending on study accrual).
- Minimum of a yearly regulatory audit.

2. Monitoring and Reporting Guidelines

The data is monitored by a DSMC monitor once a month as patients are enrolled and includes all visits through the first post-Dose Limiting Toxicity (DLT) period. At the time of dose escalation, a written report will be submitted to the DSMC Chair outlining the cohort dose, all adverse events and serious adverse event reports, and any Dose Limiting Toxicity as described in the protocol. The report will be reviewed by the DSMC Chair or qualified alternate and written authorization to proceed or a request for more information will be issued within two business days of the request. The report is then reviewed at the subsequent DSMC meeting. In the event that the committee does not concur with the DSMC Chair's decision, further study accrual is held while further investigation takes place.

The Principal Investigator at the UCSF Coordinating Center will hold the role of Study Chair. The Study Chair is responsible for the overall conduct of the study and for monitoring its safety and progress at all participating sites. The Study Chair will conduct continuous review of data and patient safety and discuss each patient's treatment at weekly UCSF Site Committee meetings. The discussions are documented in the UCSF Site Committee meeting minutes. For each dose level, the discussion will include the number of patients, significant toxicities in accordance with the protocol, doses adjustments, and observed responses.

Multicenter communication

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center will also coordinate monthly conference calls with the participating sites. The following issues will be discussed as appropriate:

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

Dose Level Considerations

The PI/Study Chair, participating investigators, and research coordinators from each site will review enrollment for each dose level cohort during the regularly scheduled conference calls. The dose level for ongoing enrollment will be confirmed for each patient scheduled to be enrolled at a site. Dose level assignments for any patient scheduled to begin treatment must be confirmed by the UCSF Coordinating Center via e-mail.

If a Dose Limiting Toxicity (DLT) arises in a patient treated at a participating site, all sites must be notified immediately by the UCSF Coordinating Center. The Study Chair has 1 business day (after first becoming aware of the event at either the UCSF Coordinating Center or the participating site) in which to report the information to all participating sites. If the DLT occurs at a participating site, the local investigator must report it to the UCSF Coordinating Center within one business day, after which the UCSF Coordinating Center will notify the other participating sites.

Adverse events reporting to the DSMC will include reports from both the UCSF Coordinating Center, as well as the participating sites. The DSMC will be responsible for monitoring all data entered in OnCore® at the UCSF Coordinating Center and the participating sites as per the study-specific guidelines listed in Appendix H. The data (i.e., redacted copies of source documents) from the participating sites will be downloaded into the PC console of OnCore prior to the monitoring visits in order for the DSMC to monitor the participating site's compliance with the protocol and FDA guidelines.

3. Review and Oversight Requirements

3.1 Adverse Event Monitoring

All clinically significant adverse events (AEs), whether or not considered to be expected or unexpected and whether or not considered to be associated with the use of study drug, will be entered into OnCore®, UCSF's Clinical Trial Management System.

Adverse Events are graded according to the Common Terminology Criteria for Adverse Events (CTCAE) as developed and revised by the Common Therapy Evaluation Program (CTEP) of the National Cancer Institute. Adverse Events are further given an assignment of attribution or relationship to treatment or medical procedure. Attribution categories are:

- **Definite** – The adverse event is clearly related to the investigational agent(s) or medical procedure.
- **Probable** – The adverse event is likely related to the investigational agent(s) or medical procedure.
- **Possible** – The adverse event may be related to the investigational agent(s) or medical procedure.
- **Unlikely** – The adverse event is doubtfully related to the investigational agent(s)or medical procedure.
- **Unrelated** – the adverse event is clearly not related to the investigational agent(s) or medical procedure.

All adverse events entered into OnCore® will be reviewed on a monthly basis at the UCSF Coordinating Center's Site Committee. All clinically significant adverse events must be reported to the UCSF Coordinating Center by the participating sites within 1 business days of becoming aware of the event. The Site Committee will review and discuss the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s) from the UCSF Coordinating Center and the participating sites.

3.2 Serious Adverse Event Reporting

By definition, an adverse event is defined as a serious adverse event (SAE) according to the following criteria:

- Death.
- Life-threatening (i.e. results in an immediate risk of death).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Permanent or significant disability/incapacity.
- Gives rise to a congenital anomaly/birth defect, or cancer, or any experience that suggests a significant hazard, contraindication, side effect, or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above.
- Event occurring in a gene therapy study.
- Event that changes the risk/benefit ratio of a study.
- Any other event the Principal Investigator judges to be serious or which would suggest a significant hazard, contraindication, side effect, or precaution.

Serious adverse event reporting will be in accordance with the UCSF IRB Regulations and Code of Federal Regulation Title 21 Part 312.32. The SAE will be reported on a Med Watch form.

UCSF IRB website for guidance in reporting serious adverse events:
https://irb.ucsf.edu/adverse-event

FDA website for guidance in reporting serious adverse events:
www.fda.gov/Safety/MedWatch/HowToReport/default.htm
Med Watch forms and information:
www.fda.gov/medwatch/getforms.htm
All serious adverse events are entered into OnCore®, as well as submitted to the IRB (per IRB guidelines) via iRIS®. All SAEs, whether expected or unexpected, must be reported to the UCSF Coordinating Center within 10 business days of becoming aware of the event or during the next scheduled conference all, whichever is sooner. The SAEs are reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings, which take place every six weeks. The date the SAE was sent to all required reporting agencies will be documented in OnCore®.

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and is determined to be possibly, probably, or definitely related either to the investigational drug or any research related procedure, the

Study Chair at the UCSF Coordinating Center or the assigned designee must be notified within 1 business day from the participating site(s) and the Study Chair must then notify the DSMC Chair or qualified alternate within 1 business day of this notification. The reporting procedure is by communication via e-mail, with a copy of the e-mail to the DSMC Manager.

3.3 Review of Adverse Event Rates

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert) is noted in the study, the Study Chair at the UCSF Coordinating Center is responsible for notifying the DSMC at the time the increased rate is identified. The report will indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator's Brochure or package insert.

If at any time the Study Chair stops enrollment or stops the study due to safety issues, the DSMC Chair and DSMC Manager must be notified within 1 business day via e-mail and the IRB must be notified via 10 business days via an iRIS Reporting Form.

Data and Safety Monitoring Committee Contacts:

[redacted] (DSMC Chair)
[redacted]
UCSF HDFCCC
San Francisco, CA 94158

DSMC Monitors
[redacted]
UCSF HDFCCC
San Francisco, CA
94143

Appendix 3 Data and Safety Monitoring Plan for a Multicenter Study (Phase II or III study)

1. Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all HDF CCC institutional clinical studies. A summary of DSMC activities for this study includes:

- Review of patient data.
- Review of serious adverse events.
- Monitoring every six months (depending on patient accrual).
- Minimum of a yearly regulatory audit.

2. Monitoring and Reporting Guidelines

All institutional Phase II or III therapeutic studies are designated with a moderate risk assessment (see Appendix H). The data is monitored by a DSMC Monitor twice per year with twenty percent of the patients monitored (or at least three patients if the calculated value is less than three).

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center will also coordinate monthly conference calls with the participating sites to communicate the review of adverse events, safety data, and other study matters.

The Principal Investigator at the UCSF Coordinating Center will hold the role of Study Chair. The Study Chair is responsible for the overall conduct of the study and for monitoring its safety and progress at all participating sites. The Study Chair will conduct continuous review of data and patient safety and discuss each patient's treatment at monthly UCSF Site Committee meetings. The discussions are documented in the UCSF Site Committee meeting minutes.

Multicenter communication

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center will also coordinate monthly conference calls with the participating sites. The following issues will be discussed as appropriate:

- Enrollment information.
- Adverse Events (i.e., new adverse events and updates on unresolved adverse events and new safety information).
- Protocol Violations.
- Other issues affecting the conduct of the study.

Adverse events reporting to the DSMC will include reports from both the UCSF Coordinating Center, as well as the participating sites. The DSMC will be responsible for monitoring all data entered in OnCore® at the UCSF Coordinating Center and the participating sites as per the study-specific guidelines listed in Appendix H. The data (i.e., copies of source documents) from

the participating sites will be downloaded into the PC console of OnCore prior to the monitoring visits in order for the DSMC to monitor the participating site's compliance with the protocol and FDA regulations.

3 Review and Oversight Requirements

3.1 Adverse Event Monitoring

All Grade 3-5 Adverse Events (AEs), regardless of being unexpected or considered to be associated with the use of the study drug will be entered into OnCore®, UCSF's Clinical Trial Management System.

Adverse Events are graded according to the Common Terminology Criteria for Adverse Events (CTCAE) as developed and revised by the Common Therapy Evaluation Program (CTEP) of the National Cancer Institute. Adverse Events are further given an assignment of attribution or relationship to treatment or medical procedure.

Attribution categories are:

- **Definite** – The adverse event is clearly related to the investigational agent(s) or medical procedure.
- **Probable** – The adverse event is likely related to the investigational agent(s) or medical procedure.
- **Possible** – The adverse event may be related to the investigational agent(s) or medical procedure.
- **Unlikely** – The adverse event is doubtfully related to the investigational agent(s) or medical procedure.
- **Unrelated** – the adverse event is clearly not related to the investigational agent(s) or medical procedure.

All Grade 3-5 adverse events entered into OnCore® will be reviewed on a monthly basis at the UCSF Site Committee meetings. All adverse events entered into OnCore® will be reviewed on a monthly basis at the UCSF Coordinating Center Site Committee meetings. All clinically significant adverse events must be reported to the UCSF Coordinating Center by the participating sites within 10 business days of becoming aware of the event or during the next scheduled monthly conference call, whichever is sooner. The UCSF Site Committee will review and discuss the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s) from the UCSF Coordinating Center and the participating sites.

3.2 Serious Adverse Event Reporting

By definition, an Adverse Event is defined as a Serious Adverse Event (SAE) according to the following criteria:

- Death.
- Life-threatening (i.e. results in an immediate risk of death).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Permanent or significant disability/incapacity.

- Gives rise to a congenital anomaly/birth defect, or cancer, or any experience that suggests a significant hazard, contraindication, side effect, or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above.
- Event occurring in a gene therapy study.
- Event that changes the risk/benefit ratio of a study.
- Any other event the Principal Investigator judges to be serious or which would suggest a significant hazard, contraindication, side effect, or precaution.

Serious Adverse Event reporting will be in accordance with the UCSF IRB Regulations and Code of Federal Regulation Title 21 Part 312.32. The SAE will be reported on a Med Watch form.

UCSF IRB website for guidance in reporting serious adverse events:
https://irb.ucsf.edu/adverse-event

FDA website for guidance in reporting serious adverse events:
www.fda.gov/Safety/MedWatch/HowToReport/default.htm

Med Watch forms and information:
www.fda.gov/medwatch/getforms.htm

All Serious Adverse Events are entered into OnCore®, as well as submitted to the IRB (per IRB guidelines) via iRIS®. All SAEs, whether expected or unexpected, must be reported to the UCSF Coordinating Center within 1 business days of becoming aware of the event. The SAEs are reviewed and monitored by the UCSF Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings, which take place every six weeks. The date the SAE was sent to all required reporting agencies will be documented in OnCore®.

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and is determined to be possibly, probably, or definitely related either to the investigational drug or any research related procedure, the Study Chair at the UCSF Coordinating Center or the assigned designee must be notified within 1 business day from the participating site(s) and the Study Chair must then notify the DSMC Chair or qualified alternate within 1 business day of this notification. The reporting procedure is by communication via phone or in person with written documentation of the one-on-one communication via e-mail, with a copy of the e-mail to the DSMC Manager.

3.3 Review of Adverse Event Rates

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert) is noted in the study, the Study Chair at the UCSF Coordinating Center is responsible for notifying the DSMC at the time the increased rate is identified. The report will indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator Brochure or package insert.

If at any time the Study Chair stops enrollment or stops the study due to safety issues, the DSMC Chair and DSMC Manager must be notified within 1 business day and the IRB must be notified within 10 business days via an iRIS Reporting Form.

Data and Safety Monitoring Committee Contacts:

[redacted]
UCSF HDFCCC
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* DSMP approved by NCI 09/February2012

Appendix 4TranslationalMedicine Methods and Statistical Analysis

Compare of inflammatory genes expression by Nanostring before and after initiation of treatment on study

RNA is isolated from FFPE tumor tissue using Qiagen RecoverAll kits. RNA is run on NanoString's Human Immunology Panel v2 as described by the vendor. Analysis of the data is performed using NSolver software provided by NanoString. Samples that do not reach NanoString's Quality Control benchmarks are removed from analysis. Counts or Log2 Fold Change from screen to a post-treatment time-point are used to compare samples.

Compare relative proportion of effector versus regulatory T-cells in pre-treatment and post-treatment tumor specimens

PBMCs are thawed, washed, and rested overnight. Cells are then stained with surface markers and viability dye. After being fixed and permeabilized, any necessary intercellular staining is performed. Cells are analyzed on a BD Biosciences LDS Fortessa X-20 and resulting data is analyzed by FlowJo (TreeStar).

Compare pre-treatment to post-treatment in cytokine expression, T-cell repertoire, clonality

To assess a patient's clonality and T cell fraction, Adaptive analysis is done on DNA isolated from PBMC or FFPE tissue sample from tumor. DNA is isolated using Qiagen RecoverAll kits.

Cytokine expression is measured in patient serum using MILLIPLEX MAP High Sensitivity Human Cytokine Magnetic Bead Kit (EMD Millipore, Billerica, MA). Analysis will be performed with weighted 5 Paramater Logistic curves produced by Luminex xPONENT software. Results (pg of analyte/mL of sample) are adjusted to pg of analyte/g of tumor and averaged to produce an average expression value.

Compare pre-treatment and post-treatment populations of immune cell populations in the peripheral blood including short-lived effector cells (SLECs) and memory T-cells

PBMCs are thawed, washed, and rested overnight. Cells are then stained with surface markers and viability dye. After being fixed cells are analyzed on a BD Biosciences LDS Fortessa X-20 and resulting data is analyzed by FlowJo (TreeStar).

Compare pre-treatment to post-treatment functional immune responses using Elispot analysis

PBMCs are thawed, washed, and rested overnight before being plated in 96-well MultiScreen Filter Plates (EMD Millipore, Billerica, MA) with applicable melanoma peptides, no peptide, or a positive control peptide. Relevant cytokines secreted from activated cells are captured on the plate and visualized using Biotin/Streptavidin binding of alkaline phosphatase conjugate (ALP) with BCIP/NBT Phosphatase Substrate (MABtech, Nacka Strand, Sweden). Plates are scanned with an ELISpot reader (Cellular Technology Limited, Shaker Heights, OH) and counted using CTL Immunospot 5.0 Analyzer software. Final counts of antigen specific cytokine-secreting cells is obtained by subtracting the number of spots in the no-antigen control wells from the test wells.

Statistical Analysis

Data from all assays are graphed and analyzed for statistical significance in GraphPad Prism software. T-tests are used to determine statistical significance for comparisons between 2 groups. ANOVA tests are used to determine statistical significance for comparisons between 3 or more groups. Significance is considered reached if the p value is at or below 0.05.