UCSF Helen Diller Family Comprehensive Cancer Center

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AN OPEN-LABEL, PHASE II, MULTICENTER STUDY OF ENHANCING PEMBROLIZUMAB RESPONSES IN MELANOMA THROUGH INTRATUMORAL PIL-12 ELECTROPORATION

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1. I agree to follow this protocol version as approved by the UCSF Protocol Review Committee (PRC), UCSF Institutional Review Board (UCSF IRB), and Data Safety Monitoring Committee (DSMC).

2. I will conduct the study in accordance with applicable UCSF IRB, 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 UCSF IRB policies, Federal, state and local laws and regulations.

UCSF Principal Investigator / Study Chair

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Principal Investigator **Site name and address**

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ABSTRACT

Title	An Open-label, Phase II, Multicenter Study of Enhancing Pembrolizumab Responses in Melanoma through Intratumoral pIL-12 Electroporation
Patient population	Patients with melanoma with progressive locally advanced or metastatic disease that is not amenable to definitive local therapy with curative intent.
Rationale for Study	Inhibition of the PD-L1/PD-1 axis with mAbs is transforming the therapeutic landscape in melanoma, with objective response rates (ORR) in the range of 20-50%. Unfortunately, even in melanoma, which is considered to be one of the most immunoresponsive types of solid tumor, the majority of patients will not respond to monotherapy with anti-PD-1 agents. These primary PD-1 nonresponders represent a significant unmet medical need that may benefit from a combination therapy tailored to the negative PD-L1 nonresponder phenotype. Combining the anti-PD-1 agent, pembrolizumab, with an agent capable of driving an effective T cell response, such as IL-12, may increase the immunogenicity and CTL activity in the nonresponder phenotype and enhance response to pembrolizumab.
Primary Objective	To assess the anti-tumor efficacy (defined as the best overall response rate using RECIST v1.1) of the combination of intratumoral pIL-12 EP and pembrolizumab in patients with melanoma who are progressing or have progressed on anti-PD-1 therapy.
Secondary Objectives	To assess safety and tolerability of the combination of intratumoral pIL-12 EP and pembrolizumab; duration of response; twenty-four week landmark progression free survival; median progression free survival; overall survival; and best overall objective response rate by immune-related Response Criteria (irRC) in melanoma patients treated with the combination of intratumoral pIL-12 EP and pembrolizumab.
Study Design	This is a multi-center, Phase II, open label, single-arm trial of intratumoral pIL-12 EP in combination with pembrolizumab in patients with melanoma. Patients will initiate treatment with pembrolizumab concurrently with the first cycle of intratumoral pIL-12 EP. Pembrolizumab will be administered at 200 mg flat dose every 3 weeks. Cycles of intratumoral pIL-12 EP (each cycle consisting of treatment on days 1, 5 and 8) will occur every 6 weeks as long as patients have accessible lesions for EP. Patients will be evaluated for response every 12 weeks by RECIST v1.1. Patients will continue on therapy if they have stable disease or better, defined under investigator evaluation at the time of disease evaluations. Therapy will be given until disease progression or unacceptable toxicity. The only exception will be those patients who experience a confirmed CR and who have been on treatment for at least 6 months; these patients may discontinue treatment at the investigator's discretion. Patients may reinitiate either therapy post- complete remission relapse if the study remains open and the patient meets the conditions outlined in the protocol. Patients will be followed continually for safety and tolerability by assessment of adverse events.
Number of patients	42 evaluable patients

Duration of Therapy	Patients may continue treatment for as long as they continue to benefit from treatment for up to 2 years or until disease progression; inter-current illness that prevents further administration of treatment; unacceptable adverse event(s); patient decision to withdraw from the study; significant patient non-compliance with protocol; general or specific changes in the patients' condition that render the patient unacceptable for further treatment in the judgment of the investigator; or those who experience a confirmed CR from the time of study entry. After 24 months, patients may continue study treatment if approved by the Principal Investigator, OncoSec Medical, and Merck. Patients may reinitiate either therapy post-complete remission relapse if the study remains open and the patient meets the conditions outlined in the protocol.
Duration of Follow up	After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 7). For subjects who discontinue for reasons other than progressive disease, every attempt should be made to continue monitoring their disease status by radiologic imaging. Monitoring should continue (1) until start of a new anti-cancer treatment, (2) until documented disease progression, or (3) until death, whichever occurs first. Radiographic imaging in follow-up may be performed as clinically indicated or per local standard of care. 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	The study is expected to reach completion ~24 months from the time the study opens to accrual. However, the study duration will depend on the rate of patient enrollment.
Study Drugs	Each treatment cycle is 3 weeks. Plasmid interleukin-12 (pIL-12) for intratumoral injection at ¼ tumor volume at concentration of 0.5 mg/mL followed by in vivo electroporation (EP) of six pulses at field strengths (E+) of 1500 V/cm and pulse width of 100 µs at 1-second intervals. A minimum of 0.1 mL pIL-12 per lesion for lesions <0.1 cm3 will be administered. Intratumoral pIL-12 EP will be administered on Days 1, 5 and 8 of every odd cycle (every 6 weeks). Pembrolizumab is a humanized mAb administered intravenously at 200 mg every 3 weeks.
Safety Assessments	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. Toxicities will be defined and graded using NCI CTCAE 4.0.
Efficacy Assessments	Overall response rate (ORR) will be evaluated using RECIST v1.1 by investigator evaluation at each re-staging assessment performed approximately every 12 weeks. An independent central review may also be employed for response evaluations. Duration of response (DOR), twenty-four week landmark progression free survival (PFS@24), median progression free survival (PFS), overall survival (OS) and ORR evaluated by immune related-Response Criteria (irRC) will also be assessed.

Unique Aspects of this Study	This is the first study to: 1. Evaluate the safety and efficacy of pIL-12 EP and any anti PD-1/PD-L1 inhibitor, including pembrolizumab. 2. Investigate the combination of a pembrolizumab and an interleukin, namely IL-12. 3. Understand the biology of transforming tumors treated with IL-12 and pembrolizumab. 4. Delineate the biology of intratumoral immune response of a PD-1 inhibitor and IL-12.

LIST OF ABBREVIATIONS

ADCC	antibody-dependent cell- mediated cytotoxicity
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASL	accessible superficial lesion
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CBC	complete blood cell (count)
CDC	complement-dependent cytotoxicity
CR	complete response
CRC	Clinical Research Coordinator
CRF	case report form
CT	computerized tomography
CTL	Cytotoxic T-lymphocytes
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
EOS	End of Study
EP	Electroporation
FCBP	female of childbearing potential

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
IDO	Indoleamine 2,3-dioxygenase
IND	investigational new drug application
IL	interleukin
irAEs	Immune-related adverse events
IRB	Institutional Review Board
irRC	immune-related Response Criteria
IT-pIL-12 EP	intratumoral plasmid IL-12 electroporated
IT	Intratumoral
IV	Intravenous
LDH	Lactate dehydrogenase
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
ORR	Overall response rate
pDC	Progrenitor dendritic cells
PD	Disease progression
pIL-12	Plasmid interleukin-12
PK	Pharmacokinetics
PR	Partial response
PRC	Protocol Review Committee (UCSF)
RBC	Red blood cell (count)
SD	Stable disease
SD	Standard deviation
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
TIL	Tumor infiltrating lymphocytes
TKI	Targeted kinase inhibitors
ULN	Upper limit of normal
WBC	White blood cell (count)

CONTENTS

1 INTRODUCTION

1.1 BACKGROUND ON INDICATION

Melanoma is one of the most dangerous forms of skin cancer and one of the seven most common cancers in the United States. Furthermore, its incidence is increasing [1]. When melanoma is caught early enough, surgical excision can be curative in the majority of Stage I and II melanomas and the overall 5-year survival rate for patients without spread to regional lymph nodes or other organs is about 98 percent in the United States [2]. At later stages, malignant melanoma remains a deadly and frequently difficult to treat cancer. The overall 5-year survival rate for patients falls to 62 percent when the disease reaches the lymph nodes and 15 percent when the disease metastasizes to distant organs [2].

Numerous chemotherapy regimens have been tested in melanoma with only modest success and limited overall survival benefit. Targeted kinase inhibitors (TKI) such as BRAF and MEK signal transduction inhibitors either alone or in combination, and immunotherapy agents such as the CTLA4 inhibitor ipilimumab are current first-line options in the metastatic setting, each of which have proven benefits. While BRAF and/or MEK inhibitors are very effective in terms of producing initial responses for approximately 50% of biomarker-positive patients, most patients will progress within 6 months and few patients have lasting responses [33]. Furthermore, the variable mechanisms of resistance to TKIs have limited the determination of effective sequenced treatment algorithms. Early immunotherapy agents such as interferon and high-dose IL-2 were of limited efficacy in the metastatic setting and had extensive toxicity limiting their overall applicability and long-term use. While immunotherapy can be extremely effective it is not able to halt the very aggressive disease that is commonplace in melanoma and does not benefit the majority of patients.

The importance of intact immune surveillance along with evidence demonstrating a correlation between tumor infiltrating lymphocytes (TILs) and favorable prognosis support continued efforts to focus on targeting pathways of T cell activation [34]. One major pathway emerging as a target for immunotherapy is the PD-1/PD-L1 axis due to the inhibition of T cell activation that is triggered through the T cell receptor upon binding of the PD-1 ligands (PD-L1 and PD-L2) to PD-1[3]. Inhibition of the PD-1/PD-L1 axis by monoclonal antibodies (mAbs) continues to be investigated as it plays a critical role in tumor immune evasion. Additionally, the presence of CD8+ T cells and the ratio of CD8+ effector T cells/FoxP3+ regulatory T cells seems to correlate with improved prognosis and long-term survival in solid malignancies such as melanoma[5,6]; thus enhancing T cell response and increasing immunogenicity continue to be of therapeutic importance in treating solid tumors.

1.2 BACKGROUND ON THE COMPOUNDS

Preclinical *in vitro* and *in vivo* experiments have shown that PD-1 and/or PD-L1 blockade using monoclonal antibodies (mAb) enhances tumor-cell specific activation, cytokine production, anti- tumor effector mechanisms, and clearance of tumor cells by the immune system [7-12].

Murine pre-clinical studies have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T cells and leads ultimately to tumor rejection. The presence of IFN-γ, granzyme B, and perforin upon blockade of the PD-1 pathway indicate local infiltration and activation of effector T cell function *in vivo* [8-10, 11,13,14].

Pembrolizumab is a potent and highly selective humanized mAb of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab contains the S228P stabilizing mutation and has no antibody-dependent cell- mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) activity.

Pembrolizumab modulates the level of interleukin-2 (IL-2), tumor necrosis factor alpha (TNFα), interferon gamma (IFN-γ), and other cytokines. The antibody potentiates existing immune responses only in the presence of antigen and does not nonspecifically activate T cells. Pembrolizumab strongly enhances T lymphocyte immune responses in cultured blood cells from healthy human donors, cancer patients, and primates. In T cell stimulation assays using human donor blood cells, the EC50 was in the range of 0.1 to 0.3 nM (see pembrolizumab Investigator Brochure).

Pembrolizumab is currently undergoing Phase III testing in advanced melanoma and lung populations. Data from the Phase I/II melanoma trials demonstrate a high rate of sustained tumor regression, with mainly grade 1 or grade 2 toxic effects[15]. The functional activity of pembrolizumab measured in an *ex vivo* SEB-induced IL-2 production assay (modulation assay) in whole blood samples from 2 cynomolgus monkey studies was used to determine the starting dose in the Phase I dose escalation study. Increased production of cytokines such as IL-2 have been generally regarded as a marker of potential anti-tumor immune activity and blocking PD-1 was found to increase this IL-2 response. The *ex vivo* IL-2 modulation assay data indicated a potency (EC50) of approximately 15 µg/mL (90% CI, 5-36 µg/mL) for pembrolizumab. Simulations based on allometrically scaled cynomolgus monkey PK parameters suggested that the target EC50 concentration of 15 µg/mL should be readily attained as trough levels at steady- state following IV dosing of 1 mg/kg pembrolizumab every 2 weeks. A 10 mg/kg every 2 weeks dose represents a 40-fold dose multiple over the no observed adverse effect level (NOAEL), see pembrolizumab Investigator's Brochure for more detail. The extended Phase I study tested 2 mg/kg and 10 mg/kg administration at either every 2 or every 3 weeks. Additional PK, safety, and efficacy analysis of completed and ongoing multi-dose trials (1 - 10mg/kg range) has determined a flat dose of 200 mg Q3W corresponding to 2.5 to 3 mg/kg is to be used for all new studies. This dose used in the expanded access program (NCT02083484) for melanoma patients who relapsed on ipilimumab was set at 2 mg/kg.

Publication of the multi-dose pembrolizumab monotherapy trial demonstrated the confirmed response rate by RECIST v1.1 in 117 patients with advanced melanoma to be 38% (95% confidence interval [CI], 25 to 44), with the highest confirmed response rate observed in the cohort that received 10 mg/kg every 2 weeks (52%, 95% CI, 38 to 66). The response rate did not differ significantly between patients who had received prior ipilimumab treatments and those who had not. Responses were durable in the majority of patients (median follow-up, 11 months among patients who had a response) and the overall median progression-free survival among 135 patients was longer than 7 months [15].

Of the 135 patients assessed in the 2013 publication of the Phase I trial, generalized symptoms including fatigue and asthenia, fever and chills, myalgias, and headaches were reported frequently but were of low grade. Rashes and pruritus were reported in 21% of the patients; grade 3 or 4 pruritus was reported in 1% of the patients, and grade 3 or 4 rash in 2%. Treatment-related pneumonitis was reported in 4% of the patients. Grade 3 or 4 elevations of aminotransferase levels were reported in 1% of the patients. Two cases of grade 3 renal failure were reported. Diarrhea was reported in 20% of the patients, with a single case of grade 3 treatment-related diarrhea. Grade 3 hyperthyroidism and grade 2 adrenal insufficiency developed in one patient. No other endocrinopathies were recorded[15]. Measures of efficacy

and safety resulting from this Phase I trial support administration of pembrolizumab in patients with advanced melanoma to achieve tumor regression without significant safety issues.

Intratumoral plasmid interleukin-12 (pIL-12) administered by *in vivo* electroporation (EP) will be added to the treatment regimen of melanoma in this trial. Interleukin-12 (IL-12) is a 70 kilodalton protein consisting of two subunits linked by a disulfide bond [36]. 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)[35-37] . Also, as a potent inducer of interferon-gamma (IFN-γ), IL-12 can drive upregulation of antigen processing and presentation machinery (APM) within tumors.

IL-12 has undergone pre-clinical testing against various tumors in mice, administered as a recombinant protein therapy and by plasmid encoding IL-12 gene therapy. Comparative studies showed IL-12 gene therapy to be as efficient as IL-12 protein therapy with far less toxic side effects [16]. Delivery of IL-12 by gene therapy has been tested for antitumor effects and safety in the poorly immunogenic and metastatic B16 murine melanoma model. Intratumoral injection of pIL-12 and intratumoral injection followed by EP have demonstrated antitumor effect and far less toxicity than other methods of gene therapy delivery.

Administration of intratumoral pIL-12 followed by EP results in significant growth delay when administered as one treatment[17] with complete tumor regression achievable in two and three treatment protocols[18,19]. EP is a physical method of delivery of compounds to tissues *in vivo* and was first reported to transfect cells *in vivo* with plasmid DNA in 1991 when reporter gene expression was seen in skin cells of mice[20]. In a study conducted by Lucas et al. in 2002, mice receiving intratumoral pIL-12 (50 μg, 1μg/μL) followed by application of six 100 μs pulses with field strength of 1500 V/cm EP on day 0 and day 7 slowed tumor growth, with 47% (8/17) showing complete regression of tumors. All mice experienced prolonged survival. Seven of the animals that showed complete regression and remained disease-free for 50 days were challenged with B16.F10 tumor cells, and 5 were resistant to tumor growth. Serum levels of IL-12 and IFN-γ were not significantly greater than expression in mice that received no treatment ($P > 0.05$). Infiltration of CD4+ and CD8+ T cells was seen in tumors five days after pIL-12 EP.

In a follow up experiment comparing a two-treatment versus three-treatment protocol, three treatments (days 0, 4 and 7) under similar treatment conditions resulted in an 80% cure rate with mice free of tumors for >100 days, statistically significant ($p<0.05$) over the 60% (9 out of 15 mice) survival rate resulting from the two-treatment protocol. When challenged with B16.F10 cells, all 12 (100%) of the disease free mice in the three-treatment groups were resistant, and eight out of nine mice (88.9%) in the two-treatment group were resistant suggesting the development of an immune memory response. These treatment protocols were further examined in multiple tumor and metastatic models. In addition, no toxicity or adverse reactions were noted in the treated mice.

To fully characterize the potential toxicity following pIL-12 EP, C57B1/6 mice with established B16.F10 melanoma tumors were treated on the three-treatment protocol and evaluated for weight change, tumor response, blood chemistry and hematology values, serum IL-12 levels and histopathologic analysis of multiple tissues. Two different concentrations (0.1 μg/μL and 1 μg/μL) of intratumoral injection of pIL-12 (50 μL) with and without EP were assessed. Focal inflammation of the kidney and focal glomerusclerosis at later time points were the abnormal findings seen at the higher dose. Symptoms associated with systemic spillage of IL-12 and corresponding increased expression of IFN-ϒ, such as

weight loss and splenomegaly were not observed. No significant serum protein IL-12 levels were seen in any group [21].

Intratumoral injection of pIL-12 followed by *in vivo* EP is currently under investigation in a multi- center Phase II trial. A Phase I trial 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 pIL-12 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].

Results from the Phase I study led to the ongoing Phase II testing of intratumoral pIL-12 (0.5 mg/mL) EP in 30 patients principally with in-transit cutaneous and subcutaneous metastatic melanoma or M1a melanoma and few patients with M1b and M1c. In this trial, one treatment cycle consists of three treatment days (days 1, 5 and 8) at 12-week intervals. Interim data from 21 patients in the Phase II trial, reported 8 of 21 patients (38%) exhibited an objective response and 11 of 18 patients with evaluable lesions (61%) experienced regression of non-injected lesions. Transient pain and inflammation at the treatment site were the most common grade 1/2 drug-related adverse events (AEs), with no grade 3/4 drug-related AEs[23]. I

n the main (1-year) portion of a Phase 2 study (OMS-I100) to assess safety, tolerability, and explore the anti-tumor activity of IT-pIL12-EP monotherapy in patients with melanoma, the overall response rate (ORR) by modified “skin” Response Evaluation Criteria in Solid Tumors (RECIST) in 23 evaluable patients was 34.8% (8/23), with 17.4% (4/23) of patients achieving a complete response (CR). The disease control rate (DCR = CR + partial response [PR] + stable disease [SD]) was 65.2% (15/23). Major (i.e., ≥30%) regression of at least 1 local lesion was seen in 64.0% (16/25) of patients. Twenty-two patients had at least one anatomically distinct lesion that was left untreated (i.e., non-injected, non-EP) in order to evaluate for an abscopal effect. Major (i.e., ≥30%) regression of at least one untreated lesion was observed in 31.8% (7/22) of patients. Further in the addendum cohort, overall response rate (ORR) by modified “skin” Response Evaluation Criteria in Solid Tumors (RECIST) in 15 evaluable patients was 40% (6/15), with all 6 patients achieving a partial response (PR). The disease control rate (DCR = CR + partial response [PR] + stable disease [SD]) was 53.3% (8/15). Major (i.e., ≥30%) regression of at least 1 local lesion was seen in 44.4% (8/20) of patients. Twenty patients had at least one anatomically distinct lesion that was left untreated (i.e., non-injected, non-EP) in order to evaluate for an abscopal effect. Major (i.e., ≥30%) regression of at least one untreated lesion was observed in 20% (5/20) of patients.

Overall, safety data with IT-pIL12-EP are available from 118 patients with malignancies, of whom 96 received IT-pIL12-EP as monotherapy (i.e., monotherapy patients) and 22 received IT-pIL12-EP in combination with pembrolizumab (i.e., combination patients).

Overall, IT-pIL12-EP was well tolerated as monotherapy. The only treatment-emergent adverse events (TEAEs) occurring at an incidence ≥ 10% among patients treated with IT-pIL12-EP as monotherapy were related to the treatment administration procedure, including procedural pain (55.2%), injection site inflammation (14.6%), and injection site discoloration (11.5%), as well as fatigue (12.5%). For most patients who experienced these events, the events were assessed by the Investigator as study drug- or procedurally-related. No patient treated with IT-pIL12-EP monotherapy experienced a serious adverse reaction (SAR) (i.e., a study drug-related serious adverse event [SAE]).

1.3 RATIONALE FOR THE PROPOSED STUDY

Inhibition of the PD-L1/PD-1 axis with mAbs is transforming the therapeutic landscape in melanoma, with objective response rates (ORR) in the range of 20-50%. Unfortunately, even in melanoma, which is considered to be one of the most immunoresponsive types of solid tumor, the majority of patients will not respond to monotherapy with anti-PD-1 agents. These primary PD-1-nonresponders represent a significant unmet medical need that may benefit from a combination therapy tailored to the PD-1-nonresponder phenotype to convert them to a PD-1- responder population.

PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B cells, T regs and Natural Killer (NK) cells [24,25]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells [26]. The ligands for PD-1 (PDL-1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types and various tumors [4, 29-31]. Patients with a brisk CD8+PD-1+ TIL population, usually seen in distinct clusters in association with PD-L1+ cells, often have a high probability of response to anti-PD-1 monotherapy. These patients benefit from a strong endogenous antitumor response, leading to the generation of cytotoxic T lymphocytes. On the other hand, the absence of significant numbers of TILs in melanoma is highly correlated with the lack of response to PD-1 therapy[27]. Combining the anti-PD-1 agent, pembrolizumab, with an agent capable of driving an effective T cell response, such as IL-12, may increase the immunogenicity in the nonresponder phenotype and enhance response to pembrolizumab.

Intratumoral injection of pIL-12 alone has demonstrated reduced tumor volume along with peritumoral and intratumoral infiltrates of CD4+ and CD8+ in the poorly immunogenic and anti- PD1 refractory B16.F10 mouse melanoma model[28]. The addition of EP to mediate gene delivery supports conversion of the low TIL/non-immunogenic mouse model into an immunogenic one, as evidenced by tumor regression associated with CD4+ and CD8+ infiltrates and rejection of subsequent tumor grafts[18,19]. The dose proportional increase in IL-12 protein expression and tumor levels of IFN-ϒ seen in the Phase I trial further demonstrate intratumoral changes post treatment. Emerging Phase II data indicate a doubling of intratumoral NK cells from pre- treatment through day 11 and at day 39, and increased frequency in activated circulating NK cells [23].

This trial will assess whether response to pembrolizumab in a preselected population of patients determined to have low TILmelanoma can improve overall response rates when treated in combination with intratumoral pIL-12 EP. Patients in part A will be selected based on their TIL status and patients in part B will be enrolled if they are progressing on PD-1 therapy.Tissue biopsies of all patients will be collected prior to enrollment to assess for study eligibility. Patients in part A will be selected based on a flow cytometric assay, quantifying intratumoral PD-$1_{hi}$$CD8_{+}$$CTLA4_{+}$ “exhausted” lymphocytes developed by investigators at UCSF[43]. The purpose of this patient pre-selection is to enrich the study population

for patients, who would be unlikely to respond to pembrolizumab as a monotherapy. Patients in part B will be eligible if they have received >/= 12 weeks of an anti-PD-1 therapy and have shown progression by RECIST by radiological confirmation or if cutaneous and subcutaneous lesions have enlarged or new lesions appeared.

This multi-center, open-label, single arm trial will evaluate in total 42 patients, comparing objective response rates with the combination of pIL-12 EP + pembrolizumab versus pembrolizumab historical control rates.

Each treatment cycle is 3 weeks. Patients will initiate treatment of pembrolizumab concurrently with the first cycle of intratumoral (IT) pIL-12 EP. Pembrolizumab will be administered at 200 mg once per treatment cycle (i.e., every 3 weeks). IT pIL-12 EP will be administered on days 1, 5 and 8 every 6 weeks (i.e., every odd cycle) as long as patients have accessible lesions for EP. Patients will be evaluated for objective response approximately every 12 weeks using RECIST v1.1 by investigator evaluation and will continue on therapy if they have stable disease or better at the time of disease evaluations. An independent central review may also be employed for response evaluations. Therapy will be given until disease progression or unacceptable toxicity for up to two years. The only exception will be those patients who experience a confirmed CR; these patients may discontinue treatment at the investigator's discretion. Patients may reinitiate either therapy post-complete remission relapse if the study remains open and the patient meets the conditions outlined in the protocol. Patients will be followed continually for safety and tolerability by assessment of adverse events.

1.4 CORRELATIVE STUDIES

1.4.1 BIOMARKERS

The primary biomarker objective is to assess the relationship between PD-L1 expression, TIL profile (IHC and gene expression), and anti-tumor activity of pIL-12 EP + pembrolizumab in patients. Investigators at UCSF have found that patients with a subset of "exhausted" TIL expressing PD-1_{hi}CD8+CTLA4+, demonstrate a diminished response rate to checkpoint blockade therapy[43].

It is hypothesized that treatment with IT pIL-12 EP will increase TIL expression and, therefore, increase the likelihood of tumor regression and response to pembrolizumab.

Response rates from the combination of IT pIL-12 EP plus pembrolizumab will be stratified by TIL status and PD-L1 IHC expression to insure that the study population is comparable to the historical control population treated with pembrolizumab as a monotherapy. The TIL/ PD-L1 status of the selected population will be confirmed retrospectively using at least one of the following assays: the PD-L1 IHC assay (clone 22C3) developed by Merck and by quantitative CD8 T cell density [42].

Other candidate biomarkers which will be investigated in the study may include, but are not limited to, the following:

- RNA and DNA profiling in biopsy tissue
- Multispectral fluorescent immunohistochemistry from immune subsets in biopsy tissue
- Quantitative RNA expression of candidate genes of interest
- Cytokine/chemokine profiles in peripheral blood
- Antigen specific cellular and humoral immune profiles in peripheral blood

Statistical details for the biomarker analyses are described in Section 8 (Statistical Considerations and Evaluation of Results). Tissue and blood samples will be collected at the time points described in Section 6 (Study Procedures and Observations).

1.4.2 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 IT pIL-12 EP. Such retrospective studies will be conducted with appropriate statistical considerations and evaluation of results as described in Section 8. Tissue and blood samples will be collected at the time points described in Section 6 (Study Procedures and Observations).

2 Objectives of the Study

2.1 Primary

- To assess the anti-tumor efficacy of the combination of intratumoral pIL-12 EP and pembrolizumab in patients with low TIL melanoma using RECIST v1.1.

2.2 Secondary

a) To assess safety and tolerability of the combination of IT pIL-12 EP and pembrolizumab.
b) To assess duration of response in melanoma patients treated with the combination of IT pIL-12 EP and pembrolizumab
c) To assess twenty-four week landmark progression free survival (PFS at 24) in melanoma patients treated with the combination of IT pIL-12 EP and pembrolizumab.
d) To assess median progression free survival (PFS) in melanoma patients treated with the combination of IT pIL-12 EP and pembrolizumab.
e) To assess overall survival (OS) in melanoma patients treated with the combination of IT pIL-12 EP and pembrolizumab.
f) To assess Best overall objective response rate determined by immune related- Response Criteria (irRC)
g) To assess patients stratified based on TIL status for the endpoints described in bullets 2a through 2f

2.3 Exploratory Objectives, Other Assessments

1) To investigate the relationship between candidate efficacy biomarkers and anti-tumor activity of IT pIL-12 EP + pembrolizumab:

a) To evaluate changes in PD-L1 expression and TIL profile post-treatment and its correlation with response to IT pIL-12 EP + pembrolizumab.
b) To investigate other biomarkers (e.g., PD-L1, interferon pathway activation, antigen presentation and processing machinery (APM) upregulation) that may correlate with tumor responses.
c) To investigate immune responses in peripheral blood (e.g., CD4/CD8 T cells, NK cells, circulating FoxP3+ cells).
d) To define presence and activity of immune cell subpopulations including but not limited to IDO+pDC, suppressor macrophages, and NK cells within tumor biopsies.

2) To explore biomarkers that inform scientific understanding of this therapeutic treatment through analysis of specimens retained for Future Biomedical Research.

2.4 ENDPOINTS

2.4.1 PRIMARY ENDPOINTS

Best overall objective response rate (ORR), CR + PR, within 24 weeks of first treatment with pIL-12 EP and pembrolizumab will be determined using RECIST v1.1 by investigator evaluation and compared against historical rates for pembrolizumab as a monotherapy in a similar population. An independent central review may also be employed for response evaluations. The response rate of patients in part A with low TIL status on the screening flow cytometric assay is estimated at 12.5% based on the assay's false negative rate in this population and the rate of pseudoprogression by RECIST of patients is part B is the same. .

2.4.2 SECONDARY ENDPOINTS

Safety and tolerability is defined by assessment of adverse events. These will be assessed using the NCI CTCAE version 4.0.

Duration of response (DOR) for those experiencing CR or PR is the number of days from the initial documentation of an objective response to the most current evaluation of that response (censored duration) or to documentation of progression.

Twenty-four week landmark progression free survival (PFS at 24) is defined as the percentage of patients, who have progressed at the 24 week time point.

Progression free survival (PFS) is defined as the duration between the date of treatment initiation to the first date of either disease progression or death.

Overall survival (OS) is defined as the duration between the date of treatment initiation to the date of death, regardless of the cause of death.

Best overall objective response rate, CR + PR, is determined by immune related-Response Criteria (irRC).

2.4.3 EXPLORATORY ENDPOINTS

Co-primary candidate biomarkers to be investigated in this study include PD-L1 expression levels assessed by IHC, and TIL profile assessed by CD8 T cell density in tumor tissue.

Changes in PD-L1 expression will be assessed pre- and post-treatment using one or both of the following immunohistochemical evaluations:

(1) the Merck developed PD-L1 IHC assay (clone22C3) with a stringent cut-off of <1% in tumor or stromal cells of the tumor environment.

(2) an assay developed by Tumeh/UCLA[42] is now being managed at the Rosenblum lab at UCSF with a low TIL cut-off of <600 CD8 cells/mm^2. If tumor samples demonstrate that the combination therapy converts tumors from low TIL to high TIL but without a corresponding increase in ORR, then the hypothesis that enhancing TILs will increase pembrolizumab efficacy can be rejected. Changes in other biomarkers and immune responses in tissue and blood will be assessed for association with clinical outcome (efficacy endpoints).

3 STUDY DESIGN

3.1 CHARACTERISTICS

This is a multi-center, Phase II, open label, single-arm trial of intratumoral pIL-12 EP in combination with pembrolizumab in patients with melanoma. The best overall objective response rate of the combination will be compared to negative PD-L1 historical rates for pembrolizumab as a monotherapy. Patients will be evaluated in 2 parts. Part A patients will be selected using a flow cytometric assay that quantifies intratumoral $PD\text{-}1^{hi}CD8^{+}CTLA4^{+}$ "exhausted" lymphocytes in the tumor. Part B will enroll patients who have or are failing pembrolizumab at least 12 weeks after starting PD-1 Antibody alone or in combination. The study will assess post-treatment increase of immunogenicity in melanomas and the enhancement of pembrolizumab responses in this population.

3.2 NUMBER OF SUBJECTS

This trial is planned for 42 evaluable patients. Patients will be evaluated in 2 parts. Part A (22 patients) will be selected using a flow cytometric assay that quantifies intratumoral PD-1hiCD8+CTLA4+ "exhausted" lymphocytes in the tumor. Part B will enroll 20 patients who have or are failing pembrolizumab at least 12 weeks after starting PD-1 antibody alone or in combination, or, who have been selected using a flow cytometric assay that quantifies intratumoral PD-1hiCD8+CTLA4+ "exhausted" lymphocytes in the tumor.

3.3 ELIGIBILITY CRITERIA

Patients must have baseline evaluations performed prior to the first dose of study drug and must meet all inclusion and exclusion criteria. Patients are intended to have an untreated lesion when there are 3 or more visible, treatable lesions present. 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

1. Patients must have histological or cytological diagnosis of melanoma with progressive locally advanced or metastatic disease that is not amenable to definitive local therapy with curative intent.

2. At least one measurable tumor accessible for intratumoral injection and EP on investigator's assessment.

3. Patients may have had prior chemotherapy or immunotherapy or radiation therapy. All prior therapies must be stopped 4 weeks prior to first dose of study treatment, with the exception of patients who have received ipilimumab, which must be stopped 6 weeks prior to first dose of study treatment. Patients are prohibited from receiving live vaccines within 30 days prior to first dose of study treatment.

4. Age ≥ 18 years

5. Part A: Patient has agreed to two newly obtained tumor biopsies and as required re-biopsies (that can be biopsied on investigator's assessment) and to providing the acquired tissue for biomarker analysis. Analysis of one of the fresh biopsy samples for $PD\text{-}1_{hi}CD8_{+}CTLA4hi$ in the $CD8+CD45_{+}$ gate based on flow cytometry will be done. A second fresh biopsy sample is required for further biomarker analysis and confirmation at a later date of low PD-L1 expression using an IHC assay for PD-L1 expression. A valid flow cytometry result is not required for study participation, but repeated biopsy for reanalysis is strongly recommended for patient with insufficient TILs in the first tissue sample.

Or

Part B: Anti-PD-1 non-responders are defined as those showing disease progression according to RECIST v1.1 after at least 12 weeks of therapy with a PD-1 antibody either alone or in combination with approved checkpoint inhibitor or targeted therapies according to their label. There is no serological requirement,

6. Life expectancy of at least 6 months.

7. ECOG performance status 0-1.

8. Adequate organ function within 4 weeks of administration of study therapy.

Lactate dehydrogenase (LDH)	<4 x upper limit of normal (ULN)
Adequate hematological function:	
Absolute neutrophil count (ANC)	≥1,500/μL
Platelets	≥100,000/μL
Hemoglobin	≥9 g/dL
Adequate hepatic function:	
Serum total bilirubin	≤1.5 x ULN **OR** Direct bilirubin ≤ ULN for patients with total bilirubin levels >1.5 ULN

AST (SGOT) and ALT (SGPT)	≤2.5 x ULN **OR** ≤5 x ULN for patients with liver metastases
Adequate renal function:	
Serum creatinine	≤1.5 x ULN
Coagulation:	
International normalized ration (INR) or Prothrombin Time (PT)	≤1.5 x ULN (Only if not using anticoagulants[1])
Activated partial thromboplastin time (aPTT)	≤1.5 x ULN (Only if not using anticoagulants[1])
[1]If patient is receiving anticoagulants, then value must be within therapeutic range for the condition that patient is being treated for.	

9. Female patient of childbearing potential has a negative serum or urine pregnancy test within 14 days prior to administration of study therapy.

10. The effects of pIL-12 EP and pembrolizumab on the developing human fetus are unknown. For this reason women of child-bearing potential (not free from menses for >2 years, post hysterectomy/oophorectomy, or surgically sterilized) must agree to use two methods of contraception, *or* abstain from heterosexual activity, during participation in study, from the time of consent through 120 days after the last dose of study therapy. The two methods must include at least one "barrier method". Barrier methods are diaphragms, cervical caps, cervical shields, male condoms, and female condoms. The second method of contraception may be another barrier method, a copper containing IUD, spermicidal foams, sponges and films, or hormone-based contraception (for example, hormone pills, hormone rings, hormone patches, hormone-releasing IUDs, or Depo Provera). Men with partners who are capable of getting pregnant must agree to use one of the barrier methods of contraception listed above during participation in the study, starting with the first dose of study drug through 120 days after the last dose of study therapy. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

11. Ability to understand a written informed consent document, and the willingness to sign and date it.

3.3.2 EXCLUSION CRITERIA

1. Patient is currently participating or has participated in a study of an investigational agent or using an investigational device within 4 weeks of administration of study therapy.

2. Patient is expected to require any other form of antineoplastic therapy while on study; including systemic chemotherapy, biological therapy, immunotherapy not specified in this protocol.

3. Patient has uveal melanoma.

4. Patient has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided they are clinically stable without the use of systemic steroids for at least 8 weeks prior to study entry.

5. Patient has risk factors for bowel obstruction or bowel perforation (examples include but not limited to a history of acute diverticulitis, intra-abdominal abscess, and abdominal carcinomatosis).

6. Patient previously had a severe hypersensitivity reaction to treatment with another mAb.

7. Patient has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis or interstitial lung disease.

8. Patient has active infection at time of study entry that require systemic antibiotics and/or

with an oral temperature of ≥ 38.3°C (100.9°F) within 5 days of first treatment.

9. Patients with electronic pacemakers or defibrillators are excluded from this study, as the effect of electroporation on these devices is unknown. Patients with lower extremity lesions may be discussed with the medical monitor.

10. Patient has an active autoimmune disease or a documented history of autoimmune disease or syndrome that requires systemic steroids or immunosuppressive agents. Patients with vitiligo or resolved childhood asthma/atopy would be exception to this rule. Patients that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Patients with hypothyroidism that is stable on hormone replacement will not be excluded from the study.

11. Patient has a medical condition that requires chronic systemic steroid therapy or requires any other form of immunosuppressive medication. However, patients using physiologic replacement doses of hydrocortisone, or its equivalent, will be considered eligible for this study; up to 20 mg hydrocortisone (or 5 mg of prednisone) in the morning and 10 mg hydrocortisone (or 2.5 mg of prednisone) in the evening.

12. Pregnant women are excluded from this study because the potential for teratogenic or abortifacient effects upon treatment with pIL-12 EP + pembrolizumab is unknown. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with pIL-12 EP + pembrolizumab breastfeeding should be discontinued if the mother is treated with pIL-12 EP + pembrolizumab.

13. Patients with symptomatic ascites or pleural effusion. A patient who is clinically stable following treatment for these conditions is eligible.

14. Patient is HCV Ab positive or HBSAg positive

3.4 DURATION OF THERAPY

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the Investigator should any untoward effect occur. In addition, a subject may be withdrawn by the Investigator or the Sponsor-Principal Investigator if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons.

In the absence of treatment delays due to adverse events, treatment may continue as long as the patient continues to benefit from the treatment or until:

- The subject or legal representative withdraws consent
- Confirmed radiographic disease progression
    - Note: For unconfirmed radiographic disease progression, patients should continue treatment at the discretion of the Investigator

- Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved.

- Inter-current illness that prevents further administration of treatment
- The subject has a confirmed positive serum or urine pregnancy test
- Unacceptable adverse event(s)
- Subject decides to withdraw from the study
- Significant patient non-compliance with protocol
- Subject was lost to follow-up
- General or specific changes in the patients' condition render the patient unacceptable for further treatment in the judgment of the Investigator.
- Patients who have a confirmed complete response by two scans ≥4 weeks apart and who have been on treatment for at least 6 months may discontinue pembrolizumab treatment at the discretion of the Investigator after receiving at least two doses beyond the initial determination of CR. Patients may enter retreatment for post-complete remission relapse ONLY if they meet defined criteria (see Section 5.1.2).
- Completed 24 months of study treatment

Note: 24 months of study medication is calculated as the interval from the date of first dose regardless of missed or skipped treatment. After 24 months, subjects may continue study treatment if approved by the Principal Investigator, OncoSec Medical, and Merck. Subjects who stop study treatment after 24 months may be eligible for up to one year of additional study treatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 5.1.2.

- Administrative reasons

3.5 Duration of Follow Up

The Safety Follow-up visit procedures are listed in Section 6 (Study Procedures and Observations). After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 7.6). For subjects who discontinue for reasons other than progressive disease, every attempt should be made to continue monitoring their disease status by radiologic imaging. Monitoring should continue (1) until start of a new anti-cancer treatment, (2) until documented disease progression, or (3) until death, whichever occurs first. Radiographic imaging in follow-up may be performed as clinically indicated or per local standard of care. Each subject will be followed for overall survival collecting data on subsequent treatments and responses where possible, until death, withdrawal of consent, or the end of the study, whichever occurs first.

3.6 Randomization Procedures

This is not a randomized trial.

3.7 STUDY TIMELINE

3.7.1 PRIMARY COMPLETION

The study will reach primary completion approximately 18 months from the time the study opens to accrual. However, primary completion will depend on the rate of patient enrollment.

3.7.2 STUDY COMPLETION

The study is anticipated to complete in ~24 months from the time the study opens to accrual. However, the study duration will depend on the rate of patient enrollment.

4 STUDY DRUGS

4.1 DESCRIPTION, SUPPLY AND STORAGE OF INVESTIGATIONAL DRUGS

The Investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

4.1.1 PLASMID INTERLEUKIN-12 (PIL-12)

Classification

DNA plasmid vector (pUMVC3-hIL-12-NGVL331, referred to as "pIL-12"), expressing IL-12 gene, contains the human IL-12 p35 and p40 subunits that are separated by an internal ribosomal entry site and are driven by a single CMV promoter.

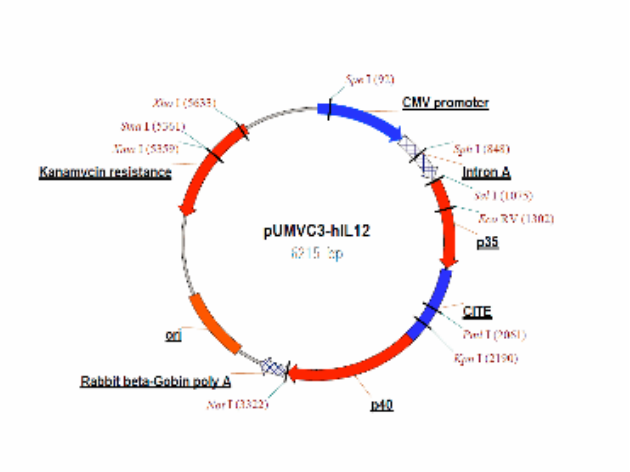


Figure 1: The structure of DNA plasmid vector expressing Interleukin-12

Mechanism of Action

pIL-12 cDNA plasmid is a nonviral, high copy number plasmid designed to achieve a transient transfection of the host cell and high level of IL-12 protein expression. EP following intratumoral pIL-12 injection delivers controlled electrical pulses in a square wave pulse pattern, yielding optimal transmembrane potential for electroporation to occur[39]. The electroporation pulses are between six hexagonal opposing needle electrodes. After the first pulse, the polarity between the opposing needle electrode pairs is reversed and the needle pair is pulsed again. After the initial paired pulse, the pulse delivery is rotated clockwise to the next opposing needle pairs until a total of six pulses are delivered to complete the electroporation sequence. Six pulses at a field strength (E+) of 1500 V/cm and pulse width of 100 µs at 1-second intervals will be administered to each previously injected tumor.

IL-12 is a 70 kilodalton protein consisting of two subunits, 40 kD and 35 kD, linked by a disulfide bond[36]. It is a potent pleotropic cytokine capable of promoting the development of a T helper 1 response, inducing the production of IFN-gamma and increasing the proliferation and cytotoxicity of NK and T

cells[37]. Studies have shown that IL-12 also acts to up-regulate the expression of HLA class I and II, and ICAM 1, on human melanoma cells, which may increase their immunogenicity. In addition, IFN increases MHC I expression on B16.F10 melanoma cells[32]. IL-12 immunotherapy also results in the inhibition of angiogenesis through mechanisms not thoroughly elucidated[38].

Contraindications

Patients may receive other medications that the Investigator deems to be medically necessary, with the specific exception of prohibited concomitant medications described in Section 6.2.3.

Availability

Plasmid interleukin-12 (pIL-12) is formulated in phosphate buffered saline (PBS) for direct intratumoral injection following by *in vivo* EP. GMP-grade pIL-12 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 1.5 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. For further, specific details of plasmid IL-12 storage, handling and preparation, please refer to the study-specific pharmacy manual. Only authorized Investigators listed on the form FDA 1572 will administer the plasmid injection and EP.

Side Effects

- Complete and updated adverse event information is available in the Investigational Drug Brochure/Investigator's Brochure.

4.1.2 PEMBROLIZUMAB

Classification

- Pembrolizumab is a potent and highly selective humanized mAb of the IfG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2.

Mechanism of Action

- Complete information is available in the Investigational Drug Brochure.

Metabolism

- Complete information is available in the Investigational Drug Brochure.

Contraindications

- Patients may receive other medications that the Investigator deems to be medically necessary, with the specific exception of prohibited concomitant medications described in Section 6.2.3.

Availability

- Clinical Supplies will be provided by Merck as summarized in Table 1.

Table 1 Product Descriptions

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

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.

Side Effects

- Complete and updated adverse event information is available in the Investigational Drug Brochure.

4.2 Drug Accountability

The investigational pharmacist or authorized designee will manage drug accountability records.

4.3 Drug Ordering

UCSF will obtain pembrolizumab directly from pharmaceutical company Merck, as study supply. The pharmaceutical company or a 3rd party vendor will supply pembrolizumab to the investigational sites (section 4.6). BioStorage Technologies, Indianapolis, IN, a biostorage vendor utilized by OncoSec Medical, will be supplying the pIL-12 to the investigational sites.

4.4 Packaging and Labeling of Study Drugs

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

4.5 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor-Principal Investigator 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.

4.6 Returns and Reconciliation

The Investigator is responsible for keeping accurate records of the clinical supplies received from Merck, OncoSec or designee, including the amount of all supplies 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.

5 TREATMENT PLAN

5.1 DOSAGE AND ADMINISTRATION

Treatment will be administered on an outpatient basis

Study Drug	Dose	Route	Schedule	Cycle Length
Pembrolizumab	200 mg	Intravenous	Day 1 for EVERY cycle	3 weeks (21 days)
pIL-12	¼ tumor volume at concentration of 0.5 mg/mL[1]	Intratumoral[2]	Days 1, 5, 8 of each odd cycle	

Note: pIL-12 should be given first followed by a 60 minute observation period between the two treatments.

1 Accessible tumors for treatment will be measured in centimeters and ¼ tumor volume will be calculated for each tumor selected for treatment: ¼ tumor volume = [(longest diameter in cm)(perpendicular diameter in cm)^2]/8; a minimum of 0.1 mL per lesion for lesions <0.1 cm^3 in ¼ volume will be administered. The maximum plasmid injection volume per patient per day will not exceed 20 mL.

2 Immediately following intratumoral injection, six pulses at field strengths (E+) of 1500 V/cm and pulse width of 100 µs at 1-second intervals will be administered to each previously injected tumor (see Section 5.1.1.1).

Thus the timing resembles

[start] Cycle 1 Pembrolizumab and pIL-12

[3weeks] Cycle 2 Pembrolizumab

[6weeks] Cycle 3 Pembrolizumab and pIL-12

[9weeks] Cycle 4 Pembrolizumab

[12weeks] Cycle 5 Pembrolizumab and pIL-12 and so forth.

5.1.1 TIMING OF DOSE ADMINISTRATION

All trial treatments are planned to be administered on an outpatient basis. Intratumoral pIL-12 should be given first followed by a minimum of 60 minutes observation period between the two treatments.

Pembrolizumab administration

Pembrolizumab should be administered on Day 1 of each cycle (±3days) after all procedures / assessments have been completed as detailed in the Study Procedures and Observations (Section 6.0), and after intratumoral IL-12-EP administration. Pembrolizumab will be administered as a 30 minute IV infusion (treatment cycle intervals may be increased due to toxicity as described in Section 5.2). Sites

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

The separate Pharmacy Manual contains specific instructions for pembrolizumab dose calculation, reconstitution, preparation of the infusion fluid, and administration.

Intratumoral pIL-12 Electroporation

Intratumoral pIL-12 followed by EP may be administered at each odd cycle as long as the subject has at least one accessible superficial lesion (ASL) for treatment. An ASL 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. In a case where a subject may have multiple ASLs, the maximum number of lesions should be treated at each cycle, keeping in mind, (1) patient tolerability, and (2) not to exceed the maximum daily dose of 20 mL. Prior to initiation of a new treatment cycle of pIL-12 EP, the Investigator will determine ASLs for treatment during that cycle. The same ASLs should be treated on each day of the cycle (i.e. Days 1, 5, 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 ASL may be treated as long as the maximum plasmid injection volume per patient per day does not exceed 20 mL. If no ASLs are present at subsequent cycles, the subject may skip that cycle of pIL-12 and continue on the study calendar. When feasible one lesion should remain untreated during Cycle 1 to permit biopsy of an untreated lesion, see Section 6.1.2.3.

5.1.2 Post-complete Remission Relapse Administration

Duration of therapy may continue until patients have a confirmed complete response by two scans ≥4 weeks apart and who have been on treatment for at least 6 months. Discontinuation of the study regimen (IT-pIL12-EP and pembrolizumab) may occur at the discretion of the Investigator after receiving at least two doses of pembrolizumab beyond the initial determination of CR.

Patients may reinitiate the full study regimen upon relapse if the study remains open and the patient meets the following conditions:

1. Stopped treatment after attaining an investigator-determined confirmed CR by RECISTv1.1
2. Was treated for at least 24 weeks with pembrolizumab before discontinuing therapy
3. Received at least two treatments with pembrolizumab beyond the date when the initial CR was declared
4. Experienced an investigator-determined progression after stopping treatment
5. Did not receive any anti-cancer treatment since the last dose of treatment
6. Have a performance status of 0 or 1 on the ECOG Performance Scale
7. Demonstrate adequate organ function as follows:

Adequate hematological function:	
Absolute neutrophil count (ANC)	≥1,500/μL
Platelets	≥100,000/μL
Hemoglobin	≥9 g/dL
Adequate hepatic function:	
Serum total bilirubin	≤1.5 x upper limit of normal (ULN) OR Direct bilirubin ≤ ULN for patients with total bilirubin levels >1.5 ULN
AST (SGOT) and ALT (SGPT)	≤2.5 x ULN OR ≤5 x ULN for patients with liver metastases
Adequate renal function:	
Serum creatinine	≤1.5 x ULN
Coagulation:	
International normalized ration (INR) or Prothrombin Time (PT)	≤1.5 x ULN (Only if not using anticoagulants[1])
Activated partial thromboplastin time (aPTT)	≤1.5 x ULN (Only if not using anticoagulants[1])

[1]If patient is receiving anticoagulants, then value must be within therapeutic range for that condition that patient is being treated for.

8. Female patient of childbearing potential should have a negative serum or urine pregnancy test within 14 days prior to receiving retreatment

9. Women of child-bearing potential (not free from menses for >2 years, post hysterectomy/oophorectomy, or surgically sterilized) must agree to use two methods of contraception, *or* abstain from heterosexual activity, during participation in study, starting with the first study treatment from the time of consent through 120 days after the last dose of study therapy. The two methods must include at least one "barrier method". Barrier methods are diaphragms, cervical caps, cervical shields, male condoms, and female condoms. The second method of contraception may be another barrier method, a copper containing IUD, spermicidal foams, sponges and films, or hormone-based contraception (for example, hormone pills, hormone rings, hormone patches, hormone- releasing IUDs, or Depo Provera). Men with partners who are capable of getting pregnant must agree to use one of the barrier methods of contraception listed above during participation in the study, starting with the first dose of study drug through 120 days after the last dose of study therapy.

Patients who restart treatment will be retreated at the same 21 day cycle length they received upon initial treatment. The assessments will follow the main study calendar and will be noted in the CRFs as "re-treatment" cycles.

5.1.3 Other Modality(ies) or Procedures

5.1.3.1 Electroporation (EP)

Prior to plasmid injection, using sterile precautions, 1% lidocaine may be injected around the lesion intended for IT-pIL-12 EP to obtain local anesthesia. In addition, the patient may be given analgesics or anxiolytics as necessary prior to or during treatment. After injecting the plasmid solution into the accessible tumor, a sterile applicator containing 6 stainless steel electrodes arranged in a circle will be placed into or around the tumor. The applicator will be connected to the power supply and six pulses at a field strength (E+) of 1500 V/cm and pulse width of 100 µs at 1-second intervals will be administered to each previously injected tumor. EP following intratumoral pIL-12 injection delivers controlled electrical pulses in a square wave pulse pattern, yielding optimal transmembrane potential for electroporation to occur [39]. The electroporation pulses are between six hexagonal opposing needle electrodes. After the first pulse, the polarity between the opposing needle electrode pairs is reversed and the needle pair is pulsed again. After the initial paired pulse, the pulse delivery is rotated clockwise to the next opposing needle pairs until a total of six pulses are delivered to complete the electroporation sequence. When multiple tumors are being injected on the same day, EP should be performed immediately after the plasmid injection for each tumor. Once a tumor has been completely treated, the next tumor can be injected with plasmid and immediately electroporated.

The OncoSec Medical System EP device used to deliver the plasmid consists of two main components: (1) a sterile disposable electrode applicator (OMS Applicator) with needle electrodes (OMS Applicator Tip) and (2) an electric pulse device, the OMS Electroporation Therapy Generator (OMS Generator). The OMS Applicator connects to the OMS Generator via a cable with a proximal connector. An OMS Electroporation Therapy Printer (OMS Printer) may be optionally used to generate a real time event log of the electroporation treatment information used during the treatment. Additional details regarding handling of the device are provided in the OncoSec Medical System Operator's Manual.

5.2 Dose Modifications and Dosing Delays

Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation.

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 Version4.0 (CTCAE v4.0).

5.2.1.1 Dose Modification

Pembrolizumab will be withheld for drug-related Grade 4 hematologic toxicities, non- hematological toxicity ≥ Grade 3 including laboratory abnormalities, and severe or life- threatening AEs as per Table 2 below.

Table 2 Dose modification guidelines for drug-related adverse event

Toxicity	Grade	Hold Pembrolizumab (Y/N)	Hold pIL-12 EP (Y/N)	Timing for restarting treatment	Dose/Schedule for restarting treatment	Discontinue Subject (after consultation with Sponsor)
Hematological Toxicity	1, 2, 3	No	No	N/A	N/A	N/A
	4	Yes	Yes	Toxicity resolves to Grade 0-1 for baseline	Restart study treatment Day 1 at the next scheduled treatment cycle. The next treatment cycle may begin sooner than scheduled per Investigator discretion following discussion with the OncoSec Medical Monitor.	Toxicity does not resolve within 12 weeks of last infusion *Permanent discontinuation should be considered for any severe or life-threatening event*
Non-hematological toxicity Note: Exception to be treated to grade 1 toxicity • Grade 2 alopecia • Grade 2 fatigue	1	No	No	N/A	N/A	N/A
	2	Consider withholding for persistent symptoms	No	Toxicity resolves to Grade 0-1 for baseline	*Clinical AE resolves within 4 weeks:* Same dose and schedule *Clinical AE does not resolve within 4 weeks:* May increase the dosing interval by 1 week for each occurrence	Toxicity does not resolve within 12 weeks of last infusion
	3, 4	Yes	No	Toxicity resolves to Grade 0-1 or baseline	Restart study treatment Day 1 at the next scheduled treatment cycle. The next treatment cycle may begin sooner than scheduled per Investigator discretion following discussion with the OncoSec Medical Monitor.	Toxicity does not resolve within 12 weeks of last infusion *Permanent discontinuation should be considered for any severe or life-threatening event*

In case toxicity does not resolve to Grade 0-1 or baseline within 12 weeks after last infusion, trial treatment should be discontinued after consultation with the Sponsor-Principal Investigator. With Investigator and Sponsor-Principal Investigator agreement, subjects with a laboratory adverse event still at Grade 2 after 12 weeks may continue treatment in the trial only if asymptomatic and controlled.

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

5.3 Monitoring and Toxicity Management

Each patient receiving IT pIL-12 EP + pembrolizumab will be evaluable for safety. 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.

Each patient will be assessed periodically for the development of any toxicity as outlined in Section 6 Study Procedures and Observations. Toxicity will be assessed according to the NCI CTCAE v4.0. Dose adjustments will be made according to the system showing the greatest degree of toxicity.

5.4 Rescue Medications & Supportive Care

5.4.1 Supportive Care Guidelines

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

Note: if after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below). Refer to Section 5.2.1 for dose modification.

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

- **Pneumonitis**:
    - For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
- Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

- **Diarrhea/Colitis**:

  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).

  - All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
  - For **Grade 2 diarrhea/colitis,** administer oral corticosteroids.
  - For **Grade 3 or 4 diarrhea/colitis,** treat with intravenous steroids followed by high dose oral steroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**
  - For **T1DM** or **Grade 3-4** Hyperglycemia
    - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
    - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

- **Hypophysitis**:
  - For **Grade 2** events, treat with 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.
  - For **Grade 3-4** events, 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**:

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

  - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
    - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.

        - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
    - **Grade 3-4** hyperthyroidism
        - Treat with an initial dose of IV corticosteroid 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.

- **Hepatic**:
    - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
        - Treat with IV or oral corticosteroids
    - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
    - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.
- **Renal Failure or Nephritis**:
    - For **Grade 2** events, treat with corticosteroids.
    - For **Grade 3-4** events, treat with systemic corticosteroids.
    - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- **Management of Infusion Reactions**: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

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

TABLE 1 INFUSION REACTION TREATMENT GUIDELINES

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
	If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

6 STUDY PROCEDURES AND OBSERVATIONS

6.1 SCHEDULE OF PROCEDURES AND OBSERVATIONS

The study-specific assessments are detailed in this section and outlined in Table 4 Schedule of Study Procedures. Screening assessments must be performed within 28 days prior to the first dose of investigational product unless otherwise noted (biopsy samples during screening may be done 90 days prior to the first dose of treatment, or at the discretion of the study sponsor). 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 ± 2 days** unless otherwise noted. Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation. Research-related biomaterials will no longer be collected/processed for patients who continue treatment beyond 24 months.

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 will 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). Data will be captured in Medidata or on paper case report forms (CRFs) maintained by the site. Data may be captured on paper CRFs for patients who continue treatment beyond 24 months. Both systems are password protected and meet HIPAA requirements.

6.1.1 PRETREATMENT PERIOD

6.1.1.1 Screening Assessments

The Screening procedures and assessments must be completed within 28 days of the Day 1 Visit unless otherwise noted.

- Baseline conditions assessment
- Baseline medications taken within 28 days of Cycle 1
- Archival tissue collection
- BRAF status
- Physical exam
- Vital signs, including:
  - blood pressure (systolic and diastolic), respiratory rate, heart rate, temperature, height, and weight
- Complete medical history including history of prior treatments and any residual toxicity relating to prior treatment

- Documentation of disease staging
- Documentation of disease evaluation by RECIST v1.1
- Photograph assessment with a ruler and bi-dimensional clinical measurements of target and non-target lesions. Photographs and measurements should be performed prior to biopsies.
- Performance status (ECOG)
- **Two newly obtained biopsies are mandatory at baseline**. One biopsy will be used for evaluation of TIL score by flow cytometry. A valid flow cytometry result is not required for study participation, but repeated biopsy for reanalysis is strongly recommended for patient with insufficient TILs in the first tissue sample. Low TIL samples will be presumed to have a low proportion of partially exhausted T cells for reporting purposes unless a second sample reveals an adequate TIL population. The second biopsy will be fixed in formalin and used for biomarker analysis in the tumor microenvironment using at least one IHC-based assay. Archival tissue should also be collected whenever available and as long as tissue has not been previously irradiated and no systemic antineoplastic therapy has been received by the patient between the time of the biopsy and the first administration of protocol therapy. Coagulation assessment must be evaluated within 24 hrs prior to all biopsy collections. Biopsy samples may be collected up to 90 days prior to the first dose of treatment, or at the discretion of the study sponsor.
- Complete blood count (CBC) with differential, including: hemoglobin, platelets, red blood cells, white blood cells, basophils (abs), eosinophils (abs), lymphocytes (abs), monocytes (abs), neutrophils (abs), hematocrit
- Blood chemistry assessment, including: sodium, potassium, chloride, calcium, phosphorus, magnesium, carbon dioxide CO_2 or bicarbonate, urea nitrogen (BUN), creatinine, uric acid, total protein, albumin, total bilirubin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), direct bilirubin, non-fasting glucose.
- Coagulation assessment, including: prothrombin time, partial thromboplastin time, and international normalized ratio (PT/PTT/INR)
- Thyroid function tests, including: thyroid-stimulating hormone (TSH), free thyroxine (FT4), T3
- Serum HIV and Hepatitis assessment, including: HIV 1/2 antibodies, Hepatitis B surface antigen (HBsAg), Hepatitis C virus RNA (qualitative).
- Serum or urine pregnancy test within 14 days prior to the start of study drug
- Urinalysis (dipstick and microscopic examination when findings are abnormal)
- Imaging (CT or PET-CT or MRI) of chest, abdomen and pelvis (and all extremities with lesions) for tumor/lesion assessment

6.1.2 TREATMENT PERIOD

6.1.2.1 Study Procedures, Cycle 1, *Day 1*

Physical Exam, ECOG, weight, complete CBC with differential, blood chemistry, and urinalysis do not need to be repeated if screening evaluations performed within 7 days of C1D1 unless a clinically significant change is suspected

- EP of intratumoral pIL-12: The majority of patients experience transient pain with electroporation that usually resolves within 5min of the treatment.
- pIL-12 EP. Intratumoral pIL-12 should be given first followed by a minimum of 60 minutes observation prior to pembrolizumab
- Infusion of pembrolizumab
- Review of concomitant medications since last visit
- Symptom-directed physical examination
- Vital signs, including: blood pressure (systolic and diastolic), respiratory rate, heart rate temperature, and weight
- Performance status
- Complete blood count (CBC) with differential, including: hemoglobin, platelets, red blood cells, white blood cells, basophils (abs), eosinophils (abs), lymphocytes (abs), monocytes (abs), neutrophils (abs), and hematocrit
- Blood chemistry assessment, including: sodium, potassium, chloride, calcium, phosphorus, magnesium, carbon dioxide CO_2 or bicarbonate, urea nitrogen (BUN), creatinine, uric acid, total protein, albumin, total bilirubin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), direct bilirubin, non-fasting glucose
- Exploratory research blood
- Research blood for future biomedical research
- Urinalysis (dipstick and microscopic examination when findings are abnormal)

6.1.2.2 Study Procedures Cycle 1, *Day 5 and Day 8*

- Evaluation of adverse events including pain assessment (conducted right before intratumoral pIL-12-EP, immediately following pIL-12 EP and approximately 5 minutes after pIL-12 EP using a 0-10 numeric pain rating scale)
- Review of concomitant medications since last visit
- Vital signs, including: blood pressure (systolic and diastolic), respiratory rate, heart rate, and temperature
- Exploratory research blood (Day 8 only)
- Research blood for future biomedical research (Day 8 only)

6.1.2.3 Study Procedures Cycle 2, *Day 1* (and Even Cycles)

- Infusion of pembrolizumab
- Evaluation of adverse events
- Review of concomitant medications since last visit
- Symptom-directed physical examination
- Vital signs, including: blood pressure (systolic and diastolic), respiratory rate, heart rate, temperature, weight
- Performance status
- Prior to treatment, a biopsy from both a treated and untreated lesion must be obtained for biomarker analysis **(Cycle 2 Only)**. A biopsy of the changing lesion(s) should be obtained for biomarker analysis, ideally at first sign of tumor change. Coagulation assessment must be evaluated within 24 hours prior to all biopsy collections
- Complete blood count (CBC) with differential, including: hemoglobin, platelets, red blood cells, white blood cells, basophils (abs), eosinophils (abs), lymphocytes (abs), monocytes (abs), neutrophils (abs), and hematocrit
- Blood chemistry assessment, including: sodium, potassium, chloride, calcium, phosphorus, magnesium, carbon dioxide CO_2 or bicarbonate), urea nitrogen (BUN), creatinine, uric acid, total protein, albumin, total bilirubin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), direct bilirubin, non-fasting glucose.
- Coagulation assessment is only required if a biopsy is planned and should be within 24 hours prior to the procedure. The coagulation assessment includes: prothrombin time, partial thromboplastin time, international normalized ratio (PT/PTT/INR)
- Thyroid function tests, including: thyroid-stimulating hormone (TSH), free thyroxine (FT4), T3
- Exploratory research blood (through 24 months of treatment)
- Research blood for future biomedical research (through 24 months of treatment)
- Urinalysis (dipstick and microscopic examination when findings are abnormal)
-

6.1.2.4 Study Procedures Cycle 3, *Day 1* (and Odd Cycles)

- pIL-12-EP: Intratumoral pIL-12 should be given first followed by a minimum 60 minutes observation prior to pembrolizumab
  - The majority of patients experience transient pain with electroporation that usually resolves usually within 5min of the treatment.
- Infusion of pembrolizumab
- Review of concomitant medications since last visit
- Symptom-directed physical examination

- Vital signs, including: blood pressure (systolic and diastolic), respiratory rate, heart rate, temperature, weight
- Performance status
- A biopsy of the changing lesion(s) should be obtained for biomarker analysis.
  - Coagulation assessment must be evaluated within 24 hours prior to all biopsy collections.
- Complete blood count (CBC) with differential, including: hemoglobin, platelets, red blood cells, white blood cells, basophils (abs), eosinophils (abs), lymphocytes (abs), monocytes (abs), neutrophils (abs), and hematocrit
- Blood chemistry assessment, including: sodium, potassium, chloride, calcium, phosphorus, magnesium, carbon dioxide CO_2 or bicarbonate, urea nitrogen (BUN), creatinine, uric acid, total protein, albumin, total bilirubin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), direct bilirubin, non-fasting glucose.
- Exploratory research blood (through 24 months of treatment)
- Research blood for Future Biomedical Research (through 24 months of treatment)
- Urinalysis (dipstick and microscopic examination when findings are abnormal)
- Photograph documentation with a ruler and bi-dimensional clinical measurements of target and non-target lesions. Photographs and measurements should be performed prior to any planned biopsies. **(every 4 cycles - within 7 days prior of Cycle)**
- Documentation of disease evaluation by RECIST v1.1 **(every 4 cycles - within 7 days prior of Cycle)**
- Imaging (CT or PET-CT or MRI) of chest, abdomen and pelvis (and all extremities with lesions) for tumor/lesion assessment **(every 4 cycles - within 7 days prior of Cycle).** .

6.1.2.5 Study Procedures Cycle 3 (and Odd Cycles), *Day 5 and Day 8*

- pIL-12 EP
  - The majority of patients experience pain with electroporation that is transient and resolves usually within 5min of the treatment.
- Review of concomitant medications since last visit
- Vital signs, including: blood pressure (systolic and diastolic), respiratory rate, heart rate, temperature
- Exploratory research blood (Day 8 only, through 24 months of treatment)
- Research blood for Future Biomedical Research (Day 8 only, through 24 months of treatment)

6.1.3 Safety Follow-Up/End of Study Visit Study Procedures

To be completed within 30 days +/- 2 days of the last dose of study drug.

- Evaluation of adverse events
- Review of concomitant medications since last visit
- Complete physical examination
- Vital signs, including: blood pressure (systolic and diastolic), respiratory rate, heart rate, temperature, weight
- Performance status
- Complete blood count (CBC) with differential, including: hemoglobin, platelets, red blood cells, white blood cells, basophils (abs), eosinophils (abs), lymphocytes (abs), monocytes (abs), neutrophils (abs), hematocrit
- Blood chemistry assessment, including: sodium, potassium, chloride, calcium, phosphorus, magnesium, carbon dioxide CO_2 or bicarbonate), urea nitrogen (BUN), creatinine, uric acid, total protein, albumin, total bilirubin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), direct bilirubin, non-fasting glucose.
- Coagulation assessment is only required if a biopsy is planned and should be within 24 hours of the procedure. The coagulation assessment includes: prothrombin time, partial thromboplastin time, international normalized ratio (PT/PTT/INR)
- Thyroid function tests, including: thyroid-stimulating hormone (TSH), free thyroxine (FT4), T3
- Urinalysis (dipstick and microscopic examination when findings are abnormal)
- Photograph documentation with a ruler and bi-dimensional clinical measurements of target and non-target lesions. Photographs and measurements are to be performed prior to any planned biopsies.
- Imaging (CT or PET-CT or MRI) of chest, abdomen and pelvis (and all extremities with lesions) for tumor/lesion assessment
- Documentation of disease evaluation by RECIST v1.1

If visit occurs within the 24 months on trial:

- A biopsy of changing lesion(s) should be obtained for biomarker analysis. If a patient discontinues for reasons other than progression, a biopsy of a malignant lesion should be obtained. Coagulation assessment must be evaluated within 24 hours prior to all biopsy collections.
- Exploratory research blood
- Research blood for future biomedical research

6.1.4 Post-treatment/Survival Follow-up Procedures

Upon completion of Safety Follow-up, all patients will enter the Survival Follow-up Phase unless they withdraw consent for further data collection. For subjects who discontinue for reasons other than progressive disease, every attempt should be made to continue monitoring their disease status by radiologic imaging. Radiologic monitoring should continue (1) until start of a new anti- cancer treatment,

(2) until documented disease progression, or (3) until death, whichever occurs first. Radiographic imaging in follow-up may be performed as clinically indicated or per local standard of care. At time of off treatment, all patients will enter survival follow-up, and patients or their caregivers will be contacted approximately every 90 days until closure of the study via a site-placed telephone call or documentation of clinic visit. Inquiries into the following will be made:

- Date of first progression (if the first progression has not occurred prior to entry in the Follow-Up Phase)
- Follow-up therapy for the treatment of melanoma (including radiation, anticancer treatment, adjuvant therapies or surgeries)
- Resolution of AEs and SAEs ongoing at the time of entry into survival follow-up
- Status (alive, no evidence of disease, alive with disease, deceased)
- Cause and date of death (if applicable)

6.1.5 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.

6.1.6 WITHDRAWAL/DISCONTINUATION

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.4 – Follow-up of Adverse Events. Subjects who a) attain a CR or b) complete 24 months of treatment with pembrolizumab may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 5.1.2. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 6.1.3) and then proceed to the Follow-Up Period of the study (described in Section 6.1.4).

Table 4 Schedule of Study Procedures

Period/Procedure	Screening	Cycle 1 (21 days ±3)			Cycle 2 and Even Cycles (21 days ±3)	Cycle 3 and Odd Cycles (21 days ±3)			Safety Follow-Up/ End of Study Visit
Study Day/Visit Day	**-28 to 0**	**1**	**5**	**8**	**1**	**1**	**5**	**8**	**Within 30 days from Last Dose**
Informed consent	X								
Baseline conditions [1]	X								
AE assessment		X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X
Archival Specimen Collection	X								
BRAF Status	X								
Treatment/Drug Administration									
Pembrolizumab		X			X	X			
pIL-12 EP		X	X	X		X	X	X	
Pain Assessment[2]		X	X	X		X	X	X	
Clinical procedures									
Physical exam[20]	X	X			X	X			X
Vital signs[3]	X	X	X	X	X	X	X	X	X
Medical history[4]	X								
Disease staging [5]	X								
Disease Evaluation by RECIST v1.1[6]	X					X[6]			X[6]
Performance status[7]	X	X			X	X			X
Biopsy[8]	X[8]				X[8]	X[8]			X[8]
Lesion Photographs and bi-dimensional clinical measurements	X[19]					X[19]			X[19]
Laboratory procedure									
CBC w/ Diff [9]	X	X			X	X			X

Blood chemistry [10]	X	X			X	X			X
Coagulation	X				X[11]	X[11]	X[11]	X[11]	X[11]
Thyroid Function[12]	X				X[12]				X
HIV, Hepatitis B and C[13]	X								
Pregnancy test (serum or urine)[14]	X								
Exploratory Research Blood[15]		X		X	X[21]	X[21]		X[21]	X[21]
Research Blood for Future Biomedical Research[15]		X		X	X[21]	X[21]		X[21]	X[21]
Urinalysis[16]	X	X			X[16]	X[16]			X
Imaging procedures									
Imaging	X[17]					X[17]			X[17, 18]

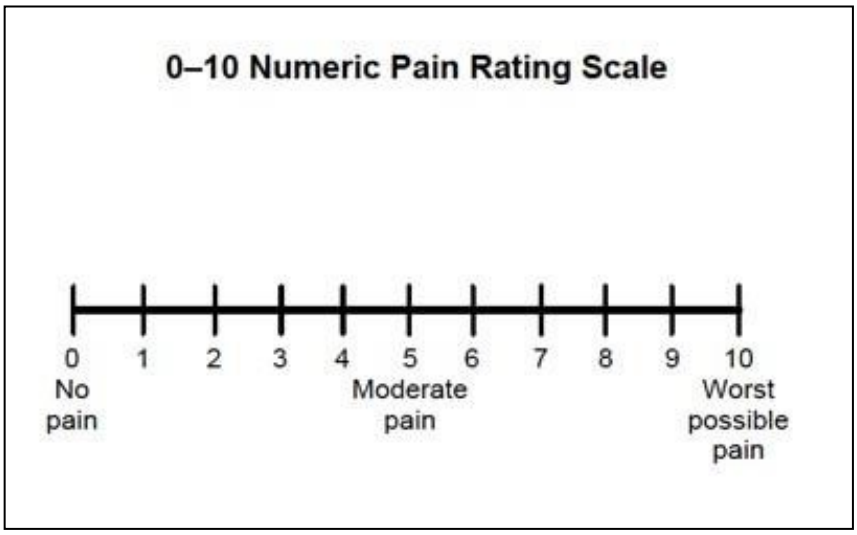
1. Baseline conditions assessment per DSMC policy (Baseline Conditions VI Form). This will only be required for patients enrolled and treated at UCSF. For other participating sites, baseline conditions will be recorded and included as part of the medical history.
2. Pain assessment monitoring will be performed as part of the adverse events assessment on Days 1, 5 and 8 of each pIL-12 EP treatment visit. Patients will use a numeric pain rating scale to rate their pain with a start and stop time to capture any pain associated with EP procedure and duration. Any pain five minutes *after* the EP treatment will be evaluated on the pain scale and documented as an AE.
3. Includes blood pressure (systolic and diastolic), respiratory rate, heart rate and temperature. Height only required at screening. Weight collected only at screening, Day 1 of every cycle, and at the Safety Follow-up/End of Study visit.
4. Medical history all cancer history and 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.
5. Disease-specific staging criteria.
6. Disease will be followed using criteria defined by RECIST v1.1. Evaluation only required at time of imaging therefore will be done every 4 cycles (within 7 days prior to Cycle 5, 9, 13, etc).
7. ECOG.
8. Two newly obtained biopsies are mandatory at baseline.
   Screening biopsy samples may be collected up to 30 days prior to the first dose of treatment, or at the discretion of the study sponsor.
   One biopsy will be used for evaluation of TIL score by flow cytometry and analysis. A valid flow cytometry result is not required for study participation, but repeated biopsy for reanalysis is strongly recommended for patient with insufficient TILs in the first tissue sample. Low TIL samples will be presumed to have a low proportion of partially exhausted T cells for reporting purposes unless a second sample reveals an adequate TIL population.
   The second biopsy will be fixed in formalin and used for biomarker analysis to confirm low PD-L1 expression in the tumor microenvironment using Merck's PD-L1 IHC assay (clone 22C3).
   At Cycle 2, prior to treatment, biopsies from both a treated and untreated lesion must be obtained for biomarker analysis. Biopsies of changing lesions should be obtained at sign of regression or progression for biomarker analysis. The biopsy techniques allowed in the study include tru cut core biopsies or surgical biopsies. Coagulation assessment must be evaluated within 24 hrs prior to all biopsy collections.
   Archival tissue may be utilized for the Merck PD-L1 assay as long as tissue has not been previously irradiated and no systemic antineoplastic therapy has been received by the patient between the time of the biopsy and the first administration of protocol therapy. However, two newly obtained biopsies at baseline are still required.
   Post-treatment biopsy should not be performed if End of Study visit occurs more than 24 months from initiation of study treatment.
   Unless noted by the PI no other biopsies are required.
9. Including hemoglobin, platelets, red blood cells, white blood cells, basophils (abs), eosinophils (abs), lymphocytes (abs), monocytes (abs), neutrophils (abs), and hematocrit.
10. Including sodium, potassium, chloride, calcium, phosphorus, magnesium, carbon dioxide CO2 or bicarbonate), urea nitrogen (BUN), creatinine, uric acid, total protein, albumin, total bilirubin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), direct bilirubin, non-fasting glucose.
11. Including PT/INR and aPTT. Coagulation assessment required if biopsies are planned and must be evaluated within 24 hrs prior to all biopsy collections, including the biopsy at Cycle 2.
12. Including T3, FT4 and TSH. Following Cycle 2, testing will be performed every other cycle (i.e., even cycles),
13. Including HIV 1/2 antibodies, HBsAg, HCV RNA (qualitative).

14. Only required for women of child-bearing potential (i.e., postmenopausal women and women who have had a hysterectomy, oophorectomy are not of child- bearing potential). Negative test must be performed within 14 days prior to first study treatment.
15. Whole blood collection for biomarker analysis. Research tubes should be collected prior to treatment.
16. Including dipstick and microscopic examinations when findings are abnormal. Following Cycle 1, testing will be performed every 3 cycles (e.g., Cycle 4, 7, 10, 13, etc.).
17. Tumor imaging (either CT or PET-CT or MRI, with strong preference for CT) will be performed within 28 days prior to enrollment. CT must be of the chest, abdomen and pelvis (and all extremities with lesions). The same imaging technique has to be used in a patient throughout the study. Imaging performed every 4 cycles, thus imaging should be performed within 7 days prior to Cycle 5, Cycle 9, Cycle 13, etc.). After first documentation of response, repeat imaging is required approximately 4 weeks later for confirmation of CR and PR.
18. The same imaging technique should be used in a patient as used earlier in the study. Assessment to be performed in patients who discontinue study therapy early without documented disease progression. Every effort should be made to continue monitoring their disease status by radiologic imaging. Monitoring should continue 1) until start of a new anti-cancer treatment, (2) until documented disease progression, or (3) until death, whichever occurs first. Radiographic imaging in follow-up may be performed as clinically indicated or per local standard of care.
19. Photograph documentation with a ruler and bi-dimensional clinical measurements of target and non-target lesions will be performed at screening, then every 4 cycles.. Photographs and clinical measurements are to be completed prior to any planned biopsies. After first documentation of response, repeat assessment is required approximately 4 weeks later for confirmation for CR and PR.
20. Screening and Safety Follow-Up/End of Study Visits should include a complete physical exam. Physical Exams at all other study time points should be symptom-directed.
21. Blood will only be collected for research through 24 months on study.

6.1.7 Criteria for Pain Assessment for AE reporting

For patients who experience pain, record start and stop time on the CRF. If pain persists beyond 5 minutes, the duration of time required for patient's post-treatment pain score to return to their baseline should be captured as an AE for pain, assessing the rating and duration (Figure 2).

Figure 2 Numeric pain rating scale



6.2 Guidelines for Biopsy Collection

Fresh tumor biopsies will be collected prior to first treatment with pIL-12-EP and at multiple time points post-treatment. Tumors biopsied at post-treatment time points may be obtained from either treated or untreated tumors as detailed below. Whenever possible, and without the risk of artifact from the screening biopsy, one of the post-treatment biopsies should be obtained from the same lesion biopsied during screening. Tumors selected for biopsy must be accessible and the procedure considered safe per the investigator. ***At any time point where a biopsy is required but the patient does not present with an accessible tumor or if a biopsy of adequate size to meet all exploratory objectives cannot be safely obtained (i.e. patient has no lesions to biopsy), this does not constitute a protocol deviation but should be clearly documented in the patient's record.*** The following guidance is provided for each biopsy time point:

Screening:

- Two biopsies (5mm punch, core or excisional biopsy) are required. A re-biopsy is permitted if results are indeterminate. Whenever possible, the second biopsy should come from the largest accessible lesion to allow for a second biopsy at Cycle 2.

Prior to Treatment Cycle 2, Day 1:

- Biopsies of both an untreated lesion and a treated lesion are required (5mm punch, core or excisional biopsy). Whenever possible, one of these biopsies should be from the same lesion as the screening biopsy if the lesion is of adequate size such that the margins of a repeat biopsy would not intersect with the margins of previous biopsy. If either lesion is too small for 5mm biopsy, please contact the investigator- sponsor.

At Safety Follow-up/ End of Study Visit

- Biopsies should be at the EOS visit whenever feasible.
- Biopsy should not be performed if EOS visit occurs more than 24 months from initiation of study treatment.

6.3 CONCOMITANT MEDICATIONS/VACCINATIONS (ALLOWED & PROHIBITED)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The Investigator should discuss any questions regarding this with the Sponsor-Principal Investigator. The final decision on any supportive therapy or vaccination rests with the Investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the Investigator, the Sponsor-Principal Investigator, and the subject.

6.3.1 ACCEPTABLE CONCOMITANT MEDICATIONS

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

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

6.3.2 PROHIBITED CONCOMITANT MEDICATIONS

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

- Anti-cancer systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab and pIL-12 EP

- Radiation therapy
  - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed after consultation with Sponsor-Principal Investigator.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.
- Glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor-Principal Investigator. Topical steroids are permitted.

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

The Exclusion Criteria describes other medications which are prohibited in this trial (described in Section 3.3.2). There are no prohibited therapies during the Post-Treatment Follow-up Phase.

6.4 DIETARY RESTRICTIONS

Patients should maintain a normal, healthy diet.

6.5 CONTRACEPTION

Pembrolizumab and/or pIL-12 EP may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab and/or pIL-12 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 signing of consent 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 Sponsor-Principal Investigator and to Merck and OncoSec Medical Inc. 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.

6.5.1 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab and/or pIL-12 EP, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor-Principal Investigator (or designee) without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor-Principal Investigator. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor-Principal Investigator (or designee) and followed as described above.

6.5.2 Use in Nursing Women

It is unknown whether pembrolizumab and/or pIL-12 is 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.

7 REPORTING AND DOCUMENTATION OF RESULTS

7.1 EVALUATION OF EFFICACY (OR ACTIVITY)

7.1.1 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. Evaluation by immune-related Response Criteria (irRC) to satisfy secondary objectives is described in Section 7.1.2.

7.1.1.1 Definitions

Evaluable for toxicity (i.e., Safety Evaluable Population)

All patients will be evaluable for toxicity from the time of their first treatment with the study drug.

Evaluable for objective response (i.e., Efficacy Evaluable Population)

Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy of both pembrolizumab and pIL-12 EP will be considered evaluable for response. These patients will have their response classified according to the definitions stated below.

7.1.1.2 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 15mm 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 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 by 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.

7.1.1.3 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.

7.1.1.4 RECIST v1.1 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 5 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

7.1.2 IMMUNE RELATED RESPONSE CRITERIA (IRRC)

Definitions of measurable and non-measurable disease

Measurable disease

Neoplastic masses that can be precisely measured in 2 in-plane perpendicular diameters. Both its longest diameter and its longest perpendicular must be greater than or equal to 10 mm or 2 times the axial slice thickness. Lymph nodes must have a short-axis line-length of ≥ 15 mm. Malignant lymph nodes must be measurable in 2 perpendicular diameters. Both its longest diameter and its longest perpendicular must be greater than or equal to 15 mm or 2 times the axial slice thickness. The quantitative endpoint will be defined as the product of the longest diameter with its longest perpendicular.

Non-measurable disease

Non-measurable lesions are those that are not suitable for quantitative assessment over time. These include:

1. Neoplastic masses that are too small to measure, because their longest uninterrupted diameter or longest perpendicular are less than 10 mm or two times the axial slice thickness.

2. Neoplastic masses whose boundaries cannot be distinguished. This includes masses which cannot be demarcated from surrounding tissue because of inadequate contrast, masses with overly complex morphology, or those with highly heterogeneous tissue composition.

3. Other types of lesions that are confidently felt to represent neoplastic tissue, but difficult to quantify in a reproducible manner. These include bone metastases, leptomeningeal metastases, malignant ascites, pleural/pericardial effusions, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, ill defined abdominal masses, etc.

For irRC, only target lesions selected at baseline and measurable new lesions are taken into account.

At the baseline tumor assessment, the sum of the products of the two largest perpendicular diameters (SPD) of all index lesions (five lesions per organ, up to 10 visceral lesions and five cutaneous index lesions) is calculated.

At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions (≥5 X 5 mm; up to 5 new lesions per organ: 5 new cutaneous lesions and 10 visceral lesions) are added together to provide the total time-point tumor burden.

Overall response using irRC:

Complete Response (irCR)

Complete disappearance of all tumor lesions (whether measureable or not, and no new lesions). CR must be confirmed by repeated, consecutive assessments made no less than 4 weeks from the date first documented.

Partial Response (irPR)

Decrease in SPD of 50% or greater by a consecutive assessment at least 4 weeks after first documentation.

Stable Disease (irSD)

Failure to meet criteria for irCR or irPR, in absence of irPD.

Progressive Disease (irPD)

At least 25% increase in SPD relative to nadir (minimum recorded tumor burden) Confirmation by a repeat, consecutive assessment no less than 4 weeks from the data first documented.

Please note other key differences between irRC and the original WHO criteria: New measurable lesions will be incorporated into the SPDNew non measurable lesions do not define progression but preclude irCR

Non-index lesions contribute to defining irCR (complete disappearance required). IrRC for the current protocol is adopted from Wolchok et al (2009).

7.2 EVALUATION OF SAFETY

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the CTCAE v4.0 for reporting of adverse events. 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.

7.2.1 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.

Definitions of Adverse Events

7.2.1.1 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. Any untoward medical occurrence prior to dosing at C1D1 will be recorded as Medical History.

7.2.1.2 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.

7.2.1.3 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.

7.2.1.4 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.

7.2.1.5 Serious

An adverse event or suspected adverse reaction is considered *serious* if, in the view of either the Investigator or Sponsor-Principal Investigator, 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
- Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Merck in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.
    - Is a new cancer (that is not a condition of the study);
    - Is associated with an overdose.

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.

7.2.1.6 Life-threatening

An adverse event or suspected adverse reaction is considered *life-threatening* if, in the view of either the Investigator or Sponsor-Principal Investigator, 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.

7.2.2 Events of Clinical Interest

Events of clinical interest for this trial include:

1. an overdose of investigational product, as defined in Section 7.6, that is not associated with clinical symptoms or abnormal laboratory results.

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

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

7.3 Recording of an Adverse Event

All adverse events, regardless of grade, will be entered into the Medidata RAVE EDC system. For the primary UCSF clinical site, 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 the study drug. Data about these events and their severity will be recorded using the NCI CTCAE v4.0. Note: satellite sites will not be required to enter the information into OnCore®.

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 Medidata RAVE (and OnCore® when appropriate) 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
	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

7.4 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.

7.5 Adverse Events Monitoring

All adverse events, whether or not unexpected, and whether or not considered to be associated with the use of the study drug(s), will be entered into Medidata Rave®, or a paper case report form, as noted above.

The Sponsor-Principal Investigator (or designee) will assess all adverse events and determine reportability requirements to the UCSF Data and Safety Monitoring Committee (DSMC) and UCSF's Institutional Review Board; 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 Medidata Rave® will be reviewed by OncoSec Medical Inc. and monitoring reports will be reviewed by the Sponsor-Principal Investigator and/or UCSF's DSMC on an ongoing basis.

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 the study drug(s).

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 approximately every six weeks.

For a detailed description of the Data and Safety Monitoring Plan for a Multicenter Phase 2 or 3 Institutional Study at the Helen Diller Comprehensive Cancer Center please refer to Appendix 2 Multicenter Institutional Studies.

7.6 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 the study drug(s) and it is determined to be related either to the study drug(s) or to a study procedure, the Sponsor-Principal 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 Institutional Review Board

> The Sponsor-Principal Investigator must report events meeting the UCSF IRB definition of "Unanticipated Problem" (UP) within 5 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-Principal 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 Sponsor-Principal Investigator must report in an IND safety report any suspected adverse reaction that is both serious and unexpected. The Sponsor-Principal 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 Sponsor-Principal 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 Sponsor-Principal 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)).

Expedited Reporting to Merck and OncoSec Medical Inc. Reporting of Overdose

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

If an adverse event(s) is associated with ("results from") the overdose of an investigational product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met and should be reported to the Sponsor-Principal Investigator (or designee) within 24 hours.

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

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor-Principal Investigator (or designee). It is then the responsibility of UCSF as the Sponsor to complete reporting to Merck Global Safety (Attn: Worldwide Product Safety; FAX 215 993-1220) and to OncoSec Medical Inc (Attn: Medical Monitor; Email: safety@oncosec.com).

Reporting of Pregnancy and Lactation

Although pregnancy and lactation are not considered adverse events, it is the responsibility of Investigators or their designees to report any pregnancy or lactation in a subject

(spontaneously reported to them) that occurs during the trial or within 120 days of completing the trial completing the trial, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All subjects and female partners of male subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor-Principal Investigator (or designee). It is then the responsibility of UCSF as the Sponsor to complete reporting to Merck Global Safety (Attn: Worldwide Product Safety; Fax: 215-993-1220) and to OncoSec Medical Inc (Attn: Medical Monitor; Email: safety@oncosec.com).

Immediate Reporting of Adverse Events

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject must be reported within 24 hours to the Sponsor-Principal Investigator and within 2 working days to Merck Global Safety and to OncoSec Medical Inc if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anti-cancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study, whether or not related to any of the investigational products, must be reported within 24 hours to the Sponsor-Principal Investigator (or designee). It is then the responsibility of UCSF as the Sponsor to complete reporting to Merck Global Safety and OncoSec Medical Inc..

Additionally, any serious adverse event, considered by an Investigator who is a qualified physician to be related to the investigational products that is brought to the attention of the Investigator at any time following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor-Principal Investigator (or designee). It is then the responsibility of UCSF as the Sponsor to complete reporting to Merck Global Safety and OncoSec Medical Inc.

SAE reports and any other relevant safety information are to be forwarded to the Sponsor- Principal Investigator (or designee). It is then the responsibility of UCSF as the Sponsor to complete reporting to Merck (Attn: Worldwide Product Safety; Fax: 215-993-1220) and OncoSec Medical Inc (Attn: Medical Monitor; Email: safety@oncosec.com).

A copy of all 15 Day Reports and Annual Progress Reports submitted as required by FDA or other local regulators will be submitted to Merck & Co., Inc. (Attn: Worldwide Product Safety;

Fax: 215-993-1220) and OncoSec Medical Inc. **(Attn: Medical Monitor; Email: safety@oncosec.com)** at the time of submission to FDA.

All subjects with serious adverse events must be followed up for outcome. A copy of these reports must also be submitted to OncoSec Medical Inc (Attn: Medical Monitor; Email: safety@oncosec.com).

Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 24 hours to the Sponsor-Principal Investigator (or designee). It is then the responsibility of UCSF as the Sponsor to complete reporting within 2 working days to Merck Global Safety (Attn: Worldwide Product Safety; FAX 215 993-1220) and to OncoSec Medical Inc (Attn: Medical Monitor; Email: mlesafety@oncosec.com).

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

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Merck product, must be reported within 24 hours to the Sponsor-Principal Investigator or his/her designee and within 24 hours to Merck Global Safety. It is then the responsibility of UCSF as the Sponsor to complete reporting to Merck Global Safety and to OncoSec Medical Inc.

See Section 7.2.2 for definitions of events of clinical interest.

Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined in this section will not be reported to Merck as described in Immediate Reporting of Adverse Events, unless there is evidence suggesting a causal relationship between the drug and the event. Any such event will be submitted to the Sponsor-Principal Investigator within 24 hours and to Merck Global Safety and and to OncoSec Medical Inc. within 2 working days either by electronic or paper media.

Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

The Sponsor-Principal Investigator will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the subjects in the trial. Any suspected endpoint which upon review is not progression of the cancer under study will be forwarded to Merck

Global Safety and to OncoSec Medical Inc. as a SAE within 2 working days of determination that the event is not progression of the cancer under study.

Hospitalization related to convenience (e.g.transportation issues etc.) will not be considered a SAE.

8 STATISTICAL CONSIDERATIONS AND EVALUATION OF RESULTS

8.1 STUDY ENDPOINTS

8.1.1 PRIMARY ENDPOINT

Best overall objective response rate (ORR), CR + PR, within 24 weeks of first treatment with pIL-12 electroporation and pembrolizumab will be determined by RECIST v1.1 and compared against historical response rates for pembrolizumab as a monotherapy in a similar population.

8.1.2 SECONDARY ENDPOINTS

Safety and tolerability is defined by assessment of adverse events. These will be assessed using the NCI CTCAE.

Duration of response (DOR) for those experiencing CR or PR is the number of days from the initial documentation of an objective response to the most current evaluation of that response (censored duration) or to documentation of progression.

Twenty-four week landmark progression free survival (PFS at 24 weeks) is defined as the % of patients who have either progressed or not progressed at 24 weeks.

Progression free survival (PFS) is defined as the duration between the date of treatment initiation to the first date of either disease progression or death.

Overall survival (OS) is defined as the duration between the date of treatment initiation to the date of death, regardless of the cause of death.

Best overall objective response rate (ORR), CR + PR, determined by immune-related Response Criteria (irRC).

8.1.3 EXPLORATORY ENDPOINTS

Co-primary candidate biomarkers to be investigated in this study include PD-L1 expression levels assessed by IHC and TIL profile assessed by CD8 T cell density in tumor tissue. Changes in PD-L1 expression will be assessed pre- and post-treatment using at least one of the following IHC-based assays: (1) the Merck developed PD-L1 IHC assay (clone 22C3) with a stringent cut-off negative of <1% in tumor or stromal cells of the tumor environment or (2) an assay developed by Tumeh/UCLA [42] with a low TIL cut-off of <600 CD8 cells/mm2. If tumor samples demonstrate that the combination therapy converts tumors from low TIL to high TIL but without a corresponding increase in ORR, then the hypothesis that enhancing TILs will increase pembrolizumab efficacy can be rejected. Changes in other biomarkers and immune responses in tissue and blood will be assessed for association with clinical outcome (efficacy endpoints).

8.1.4 STUDY DESIGN

This is a multicenter, Phase II, open-label, 42-patient single-arm trial of intratumoral pIL-12 EP in combination with pembrolizumab in patients with melanoma. Patients will be evaluated in 2 parts. Part A patients will be selected using a flow cytometric assay that quantifies intratumoral PD-1hiCD8+CTLA4+ "exhausted" lymphocytes in the tumor. Part B will enroll patients who have or are failing pembrolizumab at least 12 weeks after starting PD-1 antibody alone or in combination, or, who have been selected using a flow cytometric assay that quantifies intratumoral PD-1hiCD8+CTLA4+ "exhausted" lymphocytes in the tumor.

8.1.5 Sample Size and Power Estimate

Best ORR by RECISTv1.1 within 24 weeks is the primary efficacy endpoint for this study. Given that this preliminary study is a single-arm combination study with a historical comparator, the sample size depends upon the presumed "baseline pembrolizumab ORR" in the biomarker selected population. The assumnption was made that the false negative rate of the assay in this projected patient population defines the H_0 for the study. Based on analysis of UCSF patients treated with pembrolizumab as a monotherapy, we estimate the false negative rate of the flow cytometric assay as 12.5%. Therefore, a 42 patient study will meet the following statistical parameters: H_0 = 12.5%; H_{alt} = 30%; alpha of 0.025 (actual; one-sided test); power = 85%.

8.1.6 Replacement Policy

Patients who discontinue from the study for reasons unrelated to the study will be replaced as required for the study to meet its objectives. The decision to remove a subject/patient and to replace dropouts will documented and made jointly by the Sponsor-Principal Investigator and study statistician.

8.1.7 Accrual estimates

This study plans to complete enrollment 18 months after opening to accrual. It is estimated that roughly half of the patient population will have PD-L1-negative melanoma meeting the eligibility criteria for enrollment. Given an estimation of 100 patients that would be candidates for an anti-PD-1 therapy seen per year at the primary clinical site alone, completion of enrollment across multiple sites within 18 months can be attained. Recruitment of other clinical sites for participation in this trial further supports achievable accrual of 42 evaluable patients within 18 months.

8.2 Analyses Plans

8.2.1 Analysis Population

8.2.1.1 Primary Analysis (or Analysis of Primary Endpoints)

THE PRIMARY EFFICACY ANALYSES WILL BE BASED ON THE FULL ANALYSIS SET (FAS) POPULATION. PATIENTS WITH MEASURABLE DISEASE AT BASELINE, WHICH IS DEFINED SEPARATELY UNDER INVESTIGATOR EVALUATION, WHO RECEIVED AT LEAST ONE DOSE OF

INTRATUMORAL PIL-12-EP AND PEMBROLIZUMAB STUDY TREATMENT WILL BE INCLUDED IN THE FAS POPULATIONSAFETY ANALYSIS SETS

Safety analysis set: The safety analysis set comprises all enrolled patients who received any amount of study drug.

8.2.1.2 Secondary Analysis (or Analysis of Secondary Endpoints)

Analyses of PFS and OS are based on the All Patients as Treated (APaT) population. The APaT population consists of all patients who received at least 1 dose of intratumoral pIL-12-EP and pembrolizumab study treatment. PFS and OS will also be analyzed based on the FAS. Analysis of DOR will be based on patients that experience CR or PR at the time of disease evaluations while on study. Analyses to satisfy exploratory endpoints will be based on the All Patients as Treated (APaT) population, consisting of all patients who received at least 1 dose of study treatment.

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.

The specimens will be stored to provide a resource for studies conducted by trial partners focused on the study of biomarkers responsible for the mechanism of action and to answer emerging questions surrounding pathway involvement or other aspects of disease. It is well recognized that information obtained from additional studies conducted on clinical specimens offers greater understanding of patient response to therapy and the potential for development of novel treatments or enhanced targeted to populations with the greatest need.

8.3 EVALUATION OF SAFETY

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the NCI CTCAE v4.0 and guidance provided in Section 7.2.

8.4 INTERIM ANALYSIS AND STOPPING RULES

An interim safety analysis will be performed after 15 patients have been treated on study. If 5 of these 15 patients have had treatment-related serious adverse events as defined in the protocol, the accrual will be stopped and the study will be terminated.

8.5 CLINICAL CRITERIA FOR EARLY TRIAL TERMINATION

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

1. Quality or quantity of data recording is inaccurate or incomplete

2. Poor adherence to protocol and regulatory requirements

3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects

4. Plans to modify or discontinue the development of the study drug

5. Study meets stopping criteria per interim analysis results

6. Sponsor terminates the trial

9 STUDY MANAGEMENT

9.1 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 Sponsor-Principal 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.

9.2 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 Institutional Review Board. Prior to obtaining IRB 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.

9.3 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.

9.4 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 Sponsor- Principal 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 Sponsor-Principal 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.

9.5 Handling and Documentation of Clinical Supplies

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

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

9.6 Case Report Forms (CRFs)

The 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 electronic Case Report Forms (eCRFs) will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered onto paper CRFs or into Medidata Rave® via data entry screens for eCRFs in accordance with the CTMS study calendar, using single data entry with a secure access account. Data may be captured on paper CRFs for patients who continue treatment beyond 24 months. 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 eCRFs.

The information collected on eCRFs shall be identical to that appearing in original source documents. Source documents will be found in the patient's medical records maintained by clinical site. 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 eCRFs. The Investigator will approve all completed eCRFs to attest that the information contained on the eCRFs is true and accurate.

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

The Investigator will be responsible for ensuring the accurate capture of study data. At study completion, when the eCRFs have been declared to be complete and accurate, the database will be locked. Any changes to the data entered into the eCRFs 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 Medidata Rave® via standardized CRFs using single data entry with a secure access account. The participating site's Clinical Research Coordinator (CRC) will complete the CRFs (including any deviations) within 10 business days of the visit; the Investigator will review and approve the completed CRFs. 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.

9.7 Oversight and Monitoring Plan

OncoSec Medical Inc. will be the monitoring entity for this study. OncoSec will be monitoring the patient and regulatory data for this trial and providing the UCSF DSMC with the monitoring reports for review. The UCSF DSMC will provide monitoring oversight. 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 additional information.

9.8 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 or designee (OncoSec Medical Inc.) for Phase II studies will also coordinate, at minimum, monthly conference calls with the participating sites or more frequently as needed to discuss risk assessment. 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

9.9 Record Keeping and Record Retention

The 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 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 eCRFs, data correction forms or queries, source documents, Sponsor-Principal 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.

9.10 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.

9.11 Study Personnel Training Plan

Study personnel from all participating sub-sites (not including UCSF) must receive training from UCSF or designee (OncoSec Medical Inc.) before the site may be activated to enroll patients. This training will include, but is not limited to, protocol and GCP overview, AE reporting, proper administration of study treatments, and review of study objectives and study procedures.

10 PROTECTION OF HUMAN SUBJECTS

10.1 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.

10.2 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 MULTICENTER INSTITUTIONAL STUDY

(PHASE 2 OR 3 INSTITUTIONAL STUDY)

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

- Review of suspected adverse reactions considered "serious"

Monitoring and Reporting Guidelines

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 quarterly 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 subject safety and discuss each subject'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, 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
- 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. The data (i.e. copies of source documents) from the participating sites will be sent electronically or faxed over to the UCSF Coordinating Center prior to the monitoring visits in order for the DSMC to monitor the participating site's compliance with the protocol, patient safety, and to verify data entry.

Adverse Event Review and Monitoring

Adverse Event Monitoring

All Grade 3-5 Adverse Events, whether or not 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.

All Grade 3-5 adverse events entered into OnCore® will be reviewed on a monthly basis at the UCSF 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 quarterly 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.

In addition, all suspected adverse reactions considered "serious" must be entered in OnCore® and reported to the UCSF Coordinating Center within 1 business day. The suspected adverse reactions considered "serious" will be reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at the DSMC meeting, which take place every six (6) weeks.

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 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 contact may be by phone or e-mail.

Increase in 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), 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 via e-mail. The DSMC must receive a formal letter within 10 business days and the CHR must be notified.

Data and Safety Monitoring Committee Contacts:

DSMC Chair:	Alan Venook, MD	DSMC Monitors
Phone:	[redacted]	[redacted]
Email:	[redacted]	UCSF Helen Diller Family Comprehensive
Address:	[redacted]	Cancer Center

* DSMP approved by NCI 09/February2012

APPENDIX 3 UCSF POLICY/PROCEDURE FOR REQUIRED REGULATORY DOCUMENTS FOR A UCSF MULTICENTER INVESTIGATOR-INITIATED ONCOLOGY CLINICAL TRIALS WITH AN INVESTIGATOR HELD INVESTIGATIONAL NEW DRUG (IND)

Purpose

This policy defines the required Regulatory Documents for Single Site and Multicenter Investigator Initiated Oncology Clinical Trials at the Helen Diller Family Comprehensive Cancer Center (HDFCCC) where the Principal Investigator (PI) holds the IND.

Background

The International Conference on Harmonization (ICH) Good Clinical Practices (GCP) Guidelines define Essential Regulatory Documents as those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of data produced. These documents serve to demonstrate compliance with standards of GCP and with all applicable regulatory requirements. Filing essential documents in a timely manner can greatly assist in the successful management of a clinical trial.

The Regulatory Documents will consist of electronic files in both iMedRIS and OnCore®, as well as paper files in the Regulatory Binders for both the Coordinating Site and the Participating Site(s) in the HDFCCC Investigator Initiated Oncology Clinical Trials.

Procedures

1. HDFCCC Essential Regulatory Documents

Documents Filed in iMedRIS:

- CHR approvals for initial submission of application, all modifications, and continuing annual renewals
- Current and prior approved protocol versions with signed protocol signature page(s)
- Committee for Human Research (CHR) approval letters and Informed Consent Form(s) (ICF)
- Current and prior versions of the Investigator Brochure (IB).
- Serious Adverse Event Reporting
- Protocol Violations and Single Patient Exception (SPE) Reports to CHR with supporting fax documentation

Documents Filed in OnCore®:

- Package Insert (if the study drug is commercial) or Investigator Brochure
- Protocol Review Committee (PRC) approved protocols, protocol amendments and Summary of Changes (SOC)
- Patient handouts
- Screening/enrollment log
- Data and Safety Monitoring Committee (DSMC) monitoring reports
- OnCore® Case Report Form (CRF) completion manual

Documents Filed in Regulatory Binder:

- Completed Food and Drug Administration (FDA) 1572 document with Principal Investigator's signature
- For all Principal Investigators and Sub-Investigators listed on the FDA 1572, will need Financial Disclosure Forms, CVs, MD Licenses, Drug Enforcement Agency (DEA) Licenses, and Staff Training Documents (i.e. Collaborative Institute Training Initiative (CITI), etc.)
- Site Initiation Visit (SIV) minutes and correspondence with participating site(s).
- As applicable, approvals for Biosafety Committee, Radiation Committee, and Infusion Center
- Serious Adverse Event (SAE) reports to CHR, Merck and OncoSec Medical and
- MedWatch reporting to FDA, Merck and OncoSec Medical and
- Delegation of Authority Form
- Drug Destruction Standard Operating Procedure (SOP)
- For all laboratories listed on the FDA 1572, will need CLIA certifications, CAP certifications, lab licenses, CVs of Lab Directors, and laboratory reference ranges

2. Additional Essential Documents for Multicenter Trials for the Coordinating Center (filed in Regulatory Binder or OnCore)

- Institutional Review Board (IRB) approval letters, IRB roster, Informed Consent Form (ICF), and Health Insurance Portability and Accountability Act (HIPAA) Consent Form for the Participating Site(s)
- For all Principal Investigators and Sub-Investigators listed on the 1572 at the Participating Site(s) – Financial Disclosure Forms, CVs, MD Licenses, and Staff Training documents (i.e. Collaborative Institute Training Initiative (CITI), etc.) (for Investigational New Drug Application
- Site Initiation Visit (SIV) minutes and correspondence with Participating Site(s).
- As applicable, approvals for Biosafety Committee, Radiation Committee, and Infusion Center for the Participating Site(s)
- Protocol Violations and Single Patient Exception (SPE) reports to IRB with supporting fax documentation for Participating Site(s)
- Drug Destruction Standard Operating Procedure (SOP) for the Participating Site(s)

- Data and Safety Monitoring Committee (DSMC) monitoring reports for the Participating Site(s)
- For all laboratories listed on FDA 1572, will need CLIA certifications, CAP certifications, lab licenses, CVs of Lab Directors, and laboratory reference ranges for the Participating Site(s)
- Copy of the Data and Safety Monitoring Plan (DSMP) Monitoring Plan for all participating site(s) in Multicenter studies or Contract Research Organization (CRO) Monitoring Plan (if an outside CRO is used for the study)
- Serious Adverse Event (SAE) forms submitted to both the IRB and the Sponsor-Principal Investigator for the Participating Site(s)

27 April 2012

Required Regulatory Documents for Sub-sites Participating in a UCSF Investigator Initiated Multicenter Trial (Checklist)

Directions:

1) Fax the documents listed below to the UCSF Coordinating center at 415-514-6955 *or*

2) Scan the documents and upload to OnCore® and create a Note to File for the on-site Regulatory binder to indicate where these documents may be found

1572

- ❒ PI and Sub investigators:
  - CV and Medical license
  - Financial disclosure form
  - NIH or CITI human subject protection training certification
- ❒ Laboratories
  - CLIA and CAP
  - CV of Lab Director and Lab Licenses

Laboratory reference ranges

Local Institutional Review Board

- ❒ IRB Approval letter
- ❒ Reviewed/Approved documents
  - Protocol version date: _____
  - Informed consent version date: _____
  - Investigator Brochure version date: _____
  - HIPAA
- ❒ Current IRB Roster

Other

- ❒ Delegation of Authority Log
  - Include NIH or CITI human subject protection training certificates or GCP training certification
- ❒ Pharmacy
  - Drug destruction SOP and Policy
- ❒ Protocol signature page
- ❒ Executed sub contract

27.apr.2012