A Phase 1b Open-label Study of Pembrolizumab for Unresectable or Metastatic Basal Cell Carcinoma

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PROTOCOL HISTORY

Document History	Notes
Date: 15 September 2015	Initial protocol submitted to Stanford Scientific Review Committee (SRC), IRB, FDA, and Merck
Date: 9 November 2015	Revisions made including the following: • Title changed • Adjusted from Phase 2 to Phase 1b as a proof of concept study • Sample size increased from 12 to 13 subjects • Study calendar updated to include the capture of AEs for each visit • Serum chemistry added for each visit • Pregnancy test added to be collected at screening, End of Treatment, and as needed (PRN)
Date: 12 December 2015	Revisions made including: • Clarification provided regarding the two study arms per SRC • Clarification of number of enrolled subjects per arm • Definition of "clearly more effective" outlined on page 27
Date: 15 January 2016	SRC approval acquired pending some updates regarding outcomes. Revisions include: • Clarification to the outcomes to be reported to ClinicalTrials.gov upon completion of the study. All updated in the statistics and analysis section of the protocol
Date: 3 May 2016	Revisions include: • Exclusion Criteria 2 updated to now include exceptions for inhaled and topical steroids • Addition of Sunil Reddy, MD, as Co-Investigator • Removal of blood sampling from protocol procedures
Date: 20 October 2016	Revision includes: • Addition of Melissa Worman, MPH, CCRC, as primary study coordinator • Minor grammatical/typographical error corrections • Clarification that intraarticular, inhaled, and intralesional steroids are allowed both at screening and during treatment • Clarification that Cycle 4 biopsy can be done prior to cycle 4 based on investigator discretion as well as clinical judgement after evaluation of tumor regression pattern(s). • Addition of language regarding allowance of an LAR to provide consent
Date: 19 January 2017	Revision includes: • Removal of Melissa Worman, MPH, CCRC, as primary study coordinator • Clarification of investigational vs commercial/Access Program drug supply

Date: 9 Feb 2017	Revision includes: • Addition of Richard Brotherton RN as study coordinator • Clarification that pulse dose systemic steroids are allowed to prophylax against contrast allergies prior to and after imaging in patients with prior known contrast allergies • Removal of the clause "***only upon agreement from the Sponsor***" for inclusion criterion 5 as this is an investigator-initiated study. • Removal of the clause "…but will not be included in the formal analysis", since this study does not directly compare ARM 1 versus ARM 2 • Removal of PT/PTT/INR from protocol after screening as this is not a necessary safety monitoring parameter in the package insert • Participants may be included for the purposes of overall survival analysis if documented by a progress note by the local oncologist or other physician at the time of study end • Clarification of commercial stock of pembrolizumab after 5 cycles • Clarification of "full physical examination" as shown in study calendar
Date: 9 Mar 2017	• Reverts pembrolizumab drug supply to investigational product only, as originally described by the protocol. Removes references to pembrolizumab "commercial stock." • Change for all study visits after screening to a targeted physical examination, when a physical examination is to be performed. • Revises eligibility for the overall survival analysis to include those subjects whose status is documented by progress notes by the local oncologist or other physician at the time of study end and/or up through 2 years from enrollment
Date: 18 Oct 2017	• Addition to allow reduction of imaging frequency by 50% if disease is stable for 1 year or more during the study (in the Study Calendar)
Date: 11 Jan 2018	• Modification of protocol to allow for interim analysis • Updates study staff
Date: 22 March 2018	• Clarifies that the primary endpoint is the overall response rate (ORR) of patients with locally-advanced or metastatic basal cell carcinoma (BCC) treated with either pembrolizumab monotherapy or in combination with vismodegib. This clarification further delineates that these 2 groups will not be directly compared on the basis of the non-random allocation to treatment cohort.
Date: 26 Apr 2018	• Corrects verbiage on primary endpoint to be consistent with other locations in protocol (page 48) that all evaluable patients regardless of arm are included in the primary endpoint of ORR • Clarifies secondary endpoint is ORR for pembrolizumab monotherapy group • Clarifies additional secondary endpoint is ORR from pembro plus vismodegib group • Adds detail to the non-comparative prospective statistical design (page 51)

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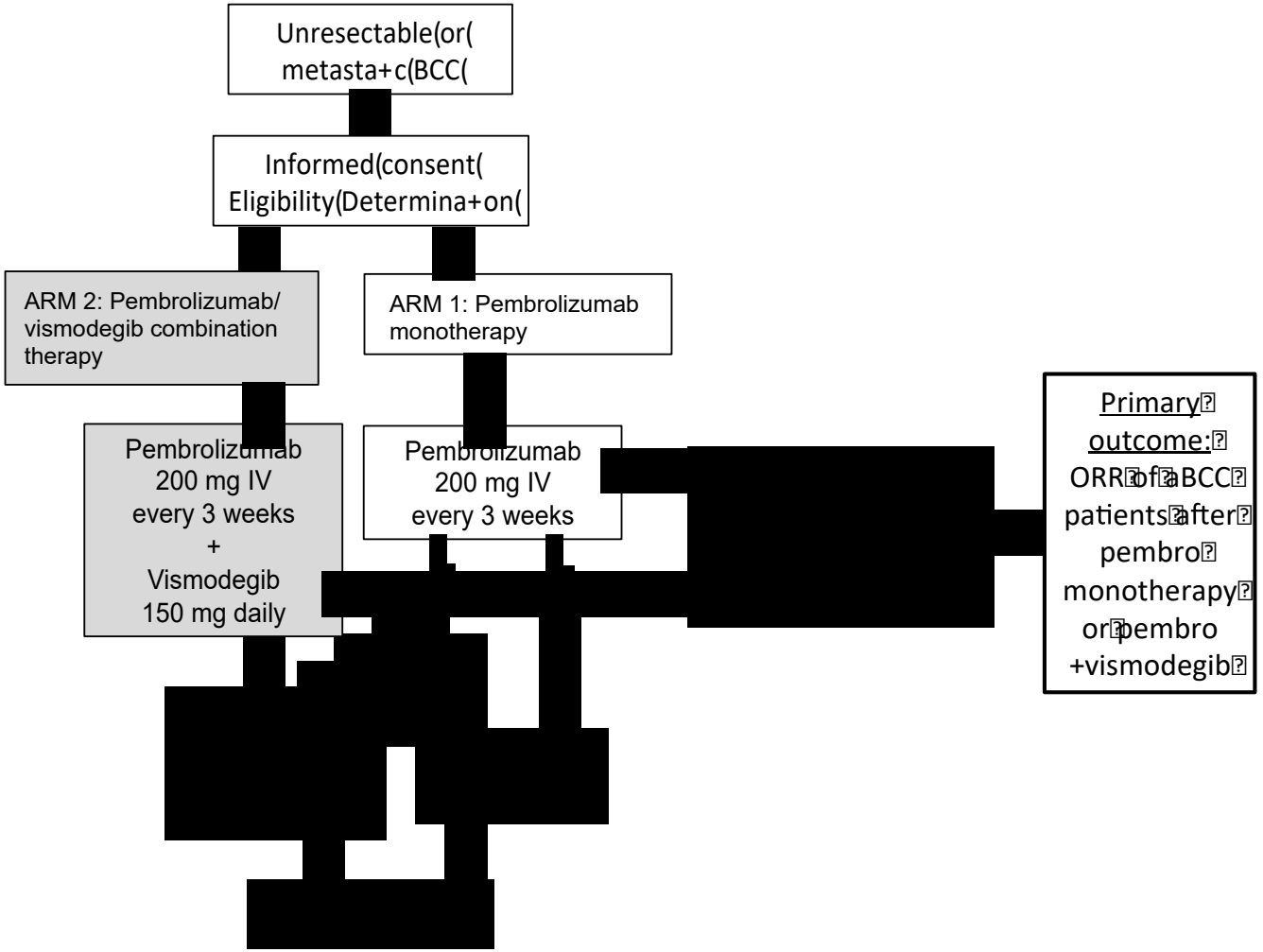
PROTOCOL SYNOPSIS

TITLE	A phase 1b open-label study of pembrolizumab for unresectable or metastatic basal cell carcinoma
STUDY PHASE	1b
INDICATION	Unresectable or metastatic basal cell carcinoma
INVESTIGATIONAL PRODUCT	Pembrolizumab
PRIMARY OBJECTIVE(S)	• Primary Objective 1: To assess the overall response rate (ORR) of unresectable or metastatic BCC patients to pembrolizumab of all evaluable patients
SECONDARY OBJECTIVE(S)	• Secondary Objective 1A: To assess the ORR of unresectable or metastatic BCC patients to pembrolizumab monotherapy • Secondary Objective 1B: To assess the ORR of unresectable or metastatic BCC patients to pembrolizumab plus vismodegib • Secondary Objective 2: To assess the safety and tolerability of pembrolizumab (either monotherapy or combination therapy) for unresectable or metastatic basal cell carcinoma • Secondary Objective 3: To assess the duration of response after pembrolizumab (either monotherapy or combination therapy) • Exploratory Objective 1: To assess the effect of pembrolizumab (either monotherapy or together with vismodegib) on the level of PDL1 and CD8 density by immunostaining • Exploratory Objective 2: To assess if pembrolizumab may improve overall survival (OS) or progression free survival (PFS) in unresectable or metastatic BCC patients (either as monotherapy or combination therapy) • Exploratory Objective 3: To assess for biomarkers that may predict response to treatment.
TREATMENT SUMMARY	Arm 1: Pembrolizumab 200 mg flat dose every 3 weeks Arm 2: Pembrolizumab 200 mg flat dose every 3 weeks + vismodegib 150 mg daily by mouth
SAMPLE SIZE	total 26 participants, approx. 13 per arm
STATISTICAL CONSIDERATIONS	*This is a proof-of-concept study, phase 1b.* Because advanced basal cells carcinoma is a rare disease, this is a non-comparative study. The primary and secondary endpoints are descriptive and the arms will not be compared. The data from this study will be used to power future multi-center studies.

SCHEMA


Unresectable(or(
metasta+c(BCC(
Informed(consent(
Eligibility(Determina+on(
ARM 2: Pembrolizumab/
vismodegib combination
therapy
ARM 1: Pembrolizumab
monotherapy
Pembrolizumab
200 mg IV
every 3 weeks
+
Vismodegib
150 mg daily
Pembrolizumab
200 mg IV
every 3 weeks
Primary
outcome:
ORR
of
aBCC
patients
after
pembro
monotherapy
or
pembro
+vismodegib

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADL	Activities of daily living
AE	Adverse event
BID	Twice daily
BSA	Body surface area
CBC	Complete blood count
CI	Confidence interval
CMAX	Maximum concentration of drug
CNS	Central nervous system
CRF	Case report/Record form
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
GI	Gastrointestinal
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
HPF	High-power field
HTN	Hypertensions
IRB	Institutional Review Board
IV	Intravenous
LLN	Lower limit of normal
OS	Overall survival
PLT	Platelet
PD	Progressive diseased
PFS	Progression free survival
PR	Partial response
QD	Once daily
RECIST	Response evaluation criteria in solid tumors
RR	Response rate
SAE	Serious adverse event
SD	Stable disease
TTP	Time to progression
ULN	Upper limit of normal
UNK	Unknown
WBC	White blood cell
WHO	World Health Organization

1. OBJECTIVES & HYPOTHESES

1.2. Primary Objective & Hypotheses

Primary Objectives	Primary Hypotheses
1: To assess the overall response rate (ORR) of unresectable or metastatic BCC patients to pembrolizumab of all evaluable patients	1: Pembrolizumab will lead to a response rate of 10% or greater in patients with advanced or metastatic basal cell carcinoma

1.2. Secondary Objectives & Hypotheses

Secondary Objectives	Secondary Hypotheses
1A and B: To compare the ORR of unresectable or metastatic BCC patients to pembrolizumab monotherapy and pembrolizumab plus vismodegib.	1: Pembrolizumab plus vismodegib will lead to a response rate of 11% or greater in patients with advanced or metastatic basal cell carcinoma for each group A) pembrolizumab monotherapy and B)pembrolizumab plus vismodegib
1: To assess the safety and tolerability of pembrolizumab (either monotherapy or combination therapy) for unresectable or metastatic basal cell carcinoma.	1: Pembrolizumab monotherapy or combination therapy is safe and well-tolerated in subjects with unresectable or metastatic basal cell carcinoma.
2. To assess the duration of response after pembrolizumab (either monotherapy or combination therapy)	2. Pembrolizumab monotherapy or combination therapy will provide a clinically-relevant duration of response (DOR)
Exploratory Objectives	**Exploratory Hypotheses**
1. To assess the effect of pembrolizumab (either monotherapy or together with vismodegib) on the level of PDL1 and CD8 density by immunostaining.	1. PDL1 levels and CD8 density will increase by immunostaining after pembrolizumab (either by monotherapy or together with vismodegib) (Topalian, *et al,* 2012)
2. To assess if pembrolizumab may improve overall survival (OS in unresectable or metastatic BCC patients (either as monotherapy or combination therapy)	2. Pembrolizumab plus vismodegib will improve OS in unresectable or metastatic BCC patients compared to pembrolizumab monotherapy.
3. To assess if possible biomarkers associated with response to treatment	3. There will be different changes in the RNA or DNA sequences detected in patient that respond to treatment compared to those that do not

2. BACKGROUND

2.1 Study Disease

Basal cell carcinomas (BCCs) are the most common cancers in humans worldwide with an estimated 77% increase over the past two decades (Mohan and Chang, 2014). Despite the staggering number of cases with over 2 million new cases per year in the United States, BCCs are understudied in large part because they are not included in the Surveillance, Epidemiology and End Results program database (Mohan and Chang, 2014).

The first-line therapy for BCCs is excision, however the five-year recurrence rate for BCC is 3% (Jarkowski, *et al,* 2014; Mohan and Chang, 2014). About 1% of BCCs are unresectable, with 28,000 cases yearly of locally advanced or metastatic disease (Mohan and Chang, 2014).

Effective therapy for unresectable BCC is a current unmet medical need. For patients with unresectable BCC, the prognosis is poor, despite recent advances in targeted therapy (Sekulic, *et al,* 2012), with >50% of patients unresponsive to Smoothened inhibitor treatment and >20% recurrence within 1 year (Chang and Oro, 2012). These patients are often referred to academic centers such as Stanford for care.

Recent advances in cancer immunotherapy open a much-needed window of opportunity to gain traction for treating unresectable BCCs. In particular, checkpoint blockade utilizing antibodies that impede immune inhibitory pathways, such as PD1/PD-L1, represent a novel strategy. The important role of the immune system in suppressing BCCs can be inferred from immunosuppressed patients who develop high rates of these cancers. One rapidly growing class of cancer immunotherapy drugs leveraging adaptive immunity is the immune checkpoint inhibitors targeting the PD1/PDL1 interaction between tumor and T cells. New emerging lines of evidence suggest that this adaptive immunotherapy for BCCs is highly likely to be effective: (1) PDL1 (also known as B7H1) overexpression in keratinocytes, which are derived from basal cells, accelerates carcinogenesis in a mouse model of CSCC (Cao, *et al,* 2011) (2) monoclonal antibodies that block PDL1 can reverse the anergic state of tumor-specific T cells leading to enhanced antitumor immunity (Lyford-Pike, *et al,* 2013) and (4) data presented at European Society for Medical Oncology 2014 revealed that an anti-PDL1 antibody (MEDI4736) for head and neck SCC (HNSCC) led to a 20% overall response rate (ORR), with a 46% response rate in PDL1 positive tumors versus 11.4% in PD-L1 negative tumors, using a cut point of 1% staining of tumor cells or stroma (Fury, *et al,* 2014; Segal, *et al,* 2014). Indeed, we have recently found that about 20-30% of advanced basal cell carcinomas stain positive for PDL1 (unpublished results), suggesting potential response of BCCs to PD1 inhibitors.

Pembrolizumab has demonstrated efficacy in melanoma and small cell lung cancer (Garon, *et al,* 2015), two cancers that are the result of environmental carcinogens, leading to a high mutational load. Similarly, BCC has been shown to be among the most mutated of human cancers, suggesting favorable response of these cancers to immunotherapy with pembrolizumab (Jayaraman, *et al,* 2014). This study is noncomparative, but there will be 2 arms, both using pembrolizumab. Because current standard of care for advanced BCC is vismodegib, a Smoothened inhibitor, despite its response rate of < 50% (Sekulic, *et al*, 2012), one of the arms in this study will be patients on vismodegib plus pembrolizumab to assess if overall response can be improved with combination therapy. In fact, in the melanoma literature, emerging data

suggests that combination chemotherapy results in improved outcomes compared to each alone (Larkin, *et al*, 2015).

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on pembrolizumab (Keytruda, MK-3475).

2.2 Study Agent

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

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). The structure of murine PD-1 has been resolved. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ; PKCθ; and ZAP70 which are involved in the CD3 T-cell signaling cascade. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda™ (pembrolizumab) has recently been approved in the United Stated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

For clinicaltrials.gov compliance

Pembrolizumab is FDA-approved for metastatic melanoma. This study requires an Investigational New Drug application (IND).

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

2.3 Rationale

Effective therapy for unresectable BCC is a current unmet medical need. For patients with unresectable BCC, the prognosis is poor, despite recent advances in targeted therapy (Sekulic, *et al,* 2012), with >50% of patients unresponsive to Smoothened inhibitor treatment and >20% recurrence within 1 year (Chang and Oro, 2012). These patients are often referred to academic centers such as Stanford for care.

Recent advances in cancer immunotherapy open a much-needed window of opportunity to gain traction for treating unresectable NMSCs.

An open-label Phase I trial (Protocol 001) is being conducted to evaluate the safety and clinical activity of single agent MK-3475 (pembrolizumab). The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of MK-3475 showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. 10 mg/kg Q2W, the highest dose tested in PN001, will be the dose and schedule utilized in Cohorts A, B, C and D of this protocol to test for initial tumor activity. Recent data from other clinical studies within the MK-3475 program has shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of MK-3475 administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (> 21 days). This early PK and pharmacodynamic data provides scientific rationale for testing a Q2W and Q3W dosing schedule.

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of MK-3475 were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. MK-3475 has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 to 5.0 for MK-3475 in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the

proposed dose regimen of 2 mg/kg Q3W (ie, 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

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

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

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

The primary endpoint will consist of evaluation of the Overall Response Rate (ORR) of all evaluable patients with unresectable or metastatic BCC including those in the pembrolizumab monotherapy group and pembrolizumab plus vismodegib combination therapy group .

Primary efficacy endpoints:

1: Overall response rate (ORR) of unresectable or metastatic BCC patients to pembrolizumab including all evaluable patients regardless of whether in pembrolizumab monotherapy or pembrolizumab vismodegib group, assessed as the percentage of patients with partial or complete response after 18 weeks of treatment (as well as 9 weeks).

Secondary endpoints):

1: ORRs of evaluable unresectable or metastatic BCC patients to A) pembrolizumab monotherapy and B) pembrolizumab plus vismodegib combination therapy, separately but not compared, as the percentage of patients with partial or complete response after 9 and 18 weeks of treatment
2. Safety and tolerability of pembrolizumab (both monotherapy or combination therapy) for unresectable or metastatic basal cell carcinoma, assessed as the percentage of treated patients experiencing adverse events of any grade, or related adverse events Grade 3 or higher, in each of the two study arms.
3. Duration of response after pembrolizumab as monotherapy and in combination with vismodegib, assessed as the median value after 9 and 18 weeks of treatment.

Exploratory endpoints:

1. Level of PDL1 and CD8 density by immunostaining in each arm of the study and overall
2. OS for each study arm and overall
3. Sequence differences in DNA and RNA of tumors responding to treatment compared to those that do not respond

2.4 Study Design

For clinicaltrials.gov and Stanford Clinical Trials Directory compliance

This is an exploratory open label, two-arm study of efficacy and safety of pembrolizumab in unresectable and/or metastatic basal cell carcinomas (BCCs. One arm will comprise individuals with unresectable or metastatic BCC who are intolerant of Smo inhibitor due to side effects, cannot use Smo inhibitor for medical cause or decline to use smoothened inhibitor monotherapy such as vismodegib. These patients will be treated with pembrolizumab until disease progression or intolerable toxicity. The second arm will comprise individuals with unresectable or metastatic BCC who are willing and able to take vismodegib together with pembrolizumab; these individuals will be treated with pembrolizumab plus vismodegib until disease progression or intolerable toxicity. Each arm will be analyzed separately.

Primary Outcome: "Overall Response Rate (ORR)" as the overall response rate (ORR) of all evaluable unresectable or metastatic BCC patients to pembrolizumab, assessed as the percentage of patients with partial or complete response after 9 and 18 weeks of treatment. This represents 3 and 6 cycles of treatment, with a cycle considered to be 3 weeks (21 days).

Secondary Outcome 1: "Overall Response Rate (ORR)" as the overall response rate (ORR) of unresectable or metastatic BCC patients to A) pembrolizumab monotherapy and B) pembrolizumab in combination with vismodegib, assessed as the percentage of patients with partial or complete response after 9 and 18 weeks of treatment.

Secondary Outcome 2: "Incidence of Adverse Events" as the percentage of treated patients by treatment cohort experiencing adverse events of any grade, or related adverse events Grade 3 or higher, in each of the two study arms

Secondary Outcome 3: "Duration of Response (DOR)" as the duration of response (DUR) to pembrolizumab as monotherapy or in combination with vismodegib, assessed as the median value (with 1st and 3rd quartiles) for subjects who complete 9 and 18 weeks of treatment.

2.5 Correlative Studies Background

Biomarkers explored will include PDL-1 levels and be performed by QualTek (Santa Barbara, CA), using formalin fixed, paraffin embedded tissue and subjected to immunohistochemistry.

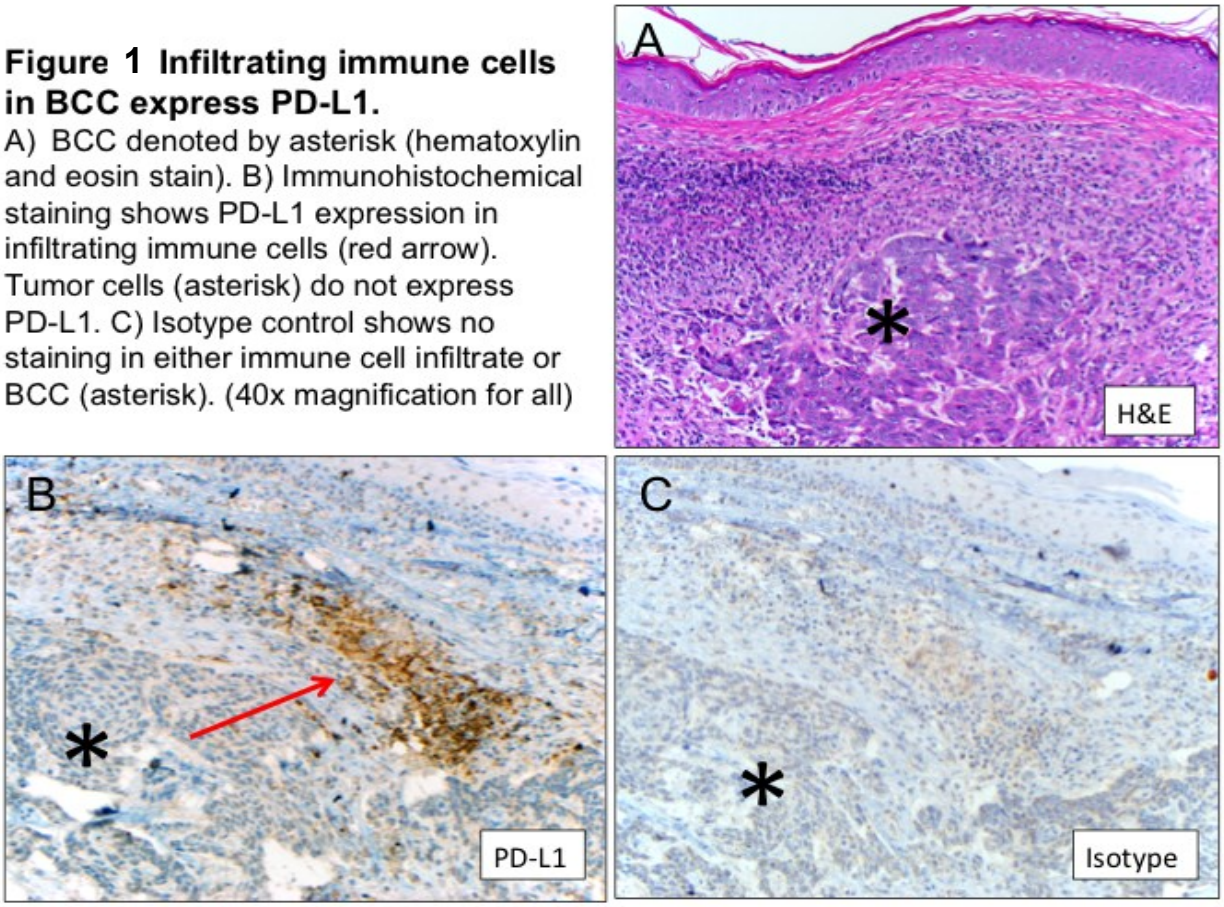
Correlatives assessed include:

- intratumoral lymphocytic infiltration pre and post treatment in each arm, including CD8+ cell density
- PDL-1 immunostaining levels pre and post treatment for each arm
- PDL-1 immunostaining levels and correlation with treatment response for each arm

Preliminary Results:

For unresectable or metastatic BCC, there are currently no clinical trials of immune checkpoint inhibitors. However, the likely response of BCCs to checkpoint inhibitors is derived from patients whose BCCs have been incidentally exposed to checkpoint inhibitors while getting treatment for metastatic melanoma. We have a patient in our clinical practice with metastatic melanoma whose advanced BCC (bracket) shrank while on a checkpoint inhibitor, but his melanoma did not (data not shown). Figure 1 shows histology of a BCC with an immune infiltrate staining for PDL1 (arrow), courtesy of J Taube). We also have unpublished results demonstrating that advanced BCCs (n = 25) show 20 to 30% positivity for PDL1 immunostaining. Correlation of this marker with clinical outcomes is currently under investigation.

Figure 1 Infiltrating immune cells in BCC express PD-L1.
A) BCC denoted by asterisk (hematoxylin and eosin stain). B) Immunohistochemical staining shows PD-L1 expression in infiltrating immune cells (red arrow). Tumor cells (asterisk) do not express PD-L1. C) Isotype control shows no staining in either immune cell infiltrate or BCC (asterisk). (40x magnification for all)



The results of our proposed study will be foundational and provide critical data to better understand the efficacy and safety of immunotherapies for unresectable or metastatic BCCs.

3. PARTICIPANT SELECTION AND ENROLLMENT PROCEDURES

Participants wishing to enter the study must be able and willing to sign written informed consent, in compliance with Stanford Human Subjects Panel and the Declaration of Helsinki principles. If a patient has a designated legally-authorized representative (LAR), the LAR can provide consent. They must fulfill the inclusion and exclusion criteria as outline below.

3.1 Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Be willing and able to provide written informed consent/assent for the trial. Consent may be obtained by LAR according to the protocol.
2. Have a histologically-proven BCC in which curative resection is unlikely without significant morbidity, or have nodal or distantly metastatic disease which has progressed on smoothened inhibitor monotherapy (ARM 1) or has undergone partial response or stable disease on smoothened inhibitor monotherapy (ARM 2). Individuals who are intolerant or have a medical contra-indication to smoothened inhibitor may be enrolled into ARM 1.
3. Be ≥ 18 years of age on day of informed consent signing.
4. Have measurable disease based on RECIST v1.1.
5. Be willing to provide tissue from a newly obtained core or excisional biopsy of a tumor lesion. *Newly-obtained is defined as a specimen obtained up to 6 weeks (42 days) prior to initiation of treatment on Day 1. Subjects for whom newly-obtained samples cannot be provided (eg, inaccessible or subject safety concern) may submit an archived specimen .*
6. Have a performance status of 0 or 1 on the ECOG Performance Scale.
7. Demonstrate adequate organ function as defined in Table 1.

Table 1. Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥ 1,500/mcL
Platelets	≥ 100,000/mcL
Hemoglobin	≥ 9 g/dL or ≥ 5.6 mmol/L without transfusion or EPO dependency (within 7 days of assessment)
Renal	
Serum creatinine **OR** Measured or calculated [a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤ 1.5 x upper limit of normal (ULN) **OR** ≥ 60 mL/min for subject with creatinine levels > 1.5 x institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 x ULN **OR** Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 x ULN **OR** ≤ 5 x ULN for subjects with liver metastases
Albumin	≥ 2.5 mg/dL
Coagulation	
International Normalized Ratio (INR) OR Prothrombin Time (PT)	≤ 1.5 x ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	≤ 1.5 X ULN unless subject is receiving anticoagulant therapy, as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a] Creatinine clearance should be calculated per institutional standard.	

8. Female subject of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the 1st dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
9. Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Section 5.7.2). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.
10. Male subjects should agree to use an adequate method of contraception starting with the 1st dose of study therapy through 120 days after the last dose of study therapy.

11. Female is not breastfeeding, is postmenopausal or surgically sterile; demonstrates non-pregnant state, and agrees to use 2 acceptable methods of birth control throughout the trial, until 120 days after the last dose of treatment
12. Male with female partner of childbearing potential agrees to use adequate method of contraception throughout study, until 120 days after last dose of treatment or last blood draw.

3.2 Exclusion Criteria

1. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the 1st dose of treatment.
2. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the 1st dose of trial treatment. Exceptions include topical, intralesional intra-articular and inhaled steroids. A pulse steroid dose prior to and after imaging to prevent contrast allergy in patients with known allergy to contrast is allowed.
3. Has a known history of active TB (Bacillus Tuberculosis)
4. Hypersensitivity to pembrolizumab or any of its excipients.
5. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to Study Day 1 or who has not recovered (ie, ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.
6. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to Study Day 1 or who has not recovered (ie, ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.
   - Note: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.
   - Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
7. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.
8. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis unless they are stable without new neurological symptoms for 1 month. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least 4 weeks prior to the 1st dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment.
9. Has active autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc) is not considered a form of systemic treatment. Intraarticular, inhaled and intralesional doses of steroids are allowed at screening and during the study.

10. Has known history of, or any evidence of active, non-infectious pneumonitis that required steroids or current pneumonitis.
11. Has an active infection requiring systemic therapy.
12. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
13. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
14. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.
15. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.
16. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1-2 antibodies).
17. Has known active Hepatitis B (eg, HBsAg reactive) or Hepatitis C (eg, HCV RNA [qualitative] is detected).
18. Has received a live vaccine within 30 days of planned start of study therapy.

Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (eg, Flu-Mist®) are live attenuated vaccines, and are not allowed.

3.3 Informed Consent Process

The Investigator must obtain documented consent from each potential subject prior to participating in a clinical trial.

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.

3.4 Treatment Assignment Procedures: All subjects will receive study treatment. There will be no randomization. Patients will be assigned to Arm 2 pembrolizumab + vismodegib only if vismodegib is a suitable treatment, otherwise they will be assigned to Arm 1 pembrolizumab only.

3.5 Study Timeline

Visit requirements are outlined in Section 6.0 Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 Trial Procedures.

3.5.1 Screening Period

The screening period will be within 28 days of Cycle 1, Day 1. Potential participants who screen fail may be rescreened, if the medical circumstances have changed.

3.5.2 Treatment Period

The treatment period will consist of 21-day cycles until disease progression as determined by RECIST 1.1 or intolerable toxicity. The treatment period is planned to be eight 21-day cycles, but treatment may be extended beyond 8 cycles if the patient has documented clinical response and treatment has been adequately tolerated. Treatment period may be interrupted for up to 21 days if there is a Grade 3 or 4 adverse event. Restarting treatment may be allowed if patient has stable disease, partial response or complete response. See also Section 3.5.7 Second Course Phase (Retreatment Period).

3.5.3 Post-Treatment Visits

There will be one post-treatment visit (end of treatment visit) will occur. If the post treatment visit occurs 30 days after the last study agent administration, it can be done on the same day as the safety follow up visit (see below). If the subject has an adverse event that is not resolved at the post-treatment visit, they will be asked to return for additional safety follow up visits until resolution of adverse events. Additional safety follow ups beyond 3 months of the end of treatment will be considered standard of care.

3.5.4 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0 to 1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded. Subjects who are eligible for retreatment with pembrolizumab (as described in Section 7.1.5.5) may have up to two safety follow-up visits, one after the Treatment Period and one after the Second Course Phase.

3.5.5 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 6 weeks (42 ± 7 days) by radiologic imaging to monitor disease status. After 1 year, the imaging time point will occur every 9 weeks (± 7 days). Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study or if the subject

begins retreatment with pembrolizumab as detailed in Section 7.1.5.5. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

Subjects who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 7.1.5.5 will move from the follow-up phase to the Second Course Phase when they experience disease progression. Details are provided in Section 6.2 Trial Flow Chart for Retreatment.

3.5.6 Survival Follow-up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted by telephone 12 weeks after end of treatment to assess for resolution of adverse events and survival status. Participants who are followed by local oncologists or other physician may be included for the purposes of overall survival analysis if documented by a progress note at the time of study completion.

3.5.7 Second Course Phase (Retreatment Period)

Subjects who stop pembrolizumab with SD or better may be eligible for up to 1 year of additional pembrolizumab therapy if they progress after stopping study treatment. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the subject meets the following conditions:

- **Either**
  - Stopped initial treatment with pembrolizumab after attaining an investigator-determined confirmed CR according to RECIST 1.1, and
    - Was treated for at least 24 weeks with pembrolizumab before discontinuing therapy
    - Received at least 2 treatments with pembrolizumab beyond the date when the initial CR was declared

  OR
  - Had SD, PR or CR and stopped pembrolizumab treatment after 24 months of study therapy for reasons other than disease progression or intolerability

AND

- Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with pembrolizumab
- Did not receive any anti-cancer treatment since the last dose of pembrolizumab
- Has a performance status of 0 or 1 on the ECOG Performance Scale
- Demonstrates adequate organ function as detailed in Section 5.1.2
- Female subject of childbearing potential should have a negative serum or urine pregnancy test within 72 hours prior to receiving retreatment with study medication.
- Female subject of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Section 5.7.2). Subjects of child bearing potential are those who have not been surgically sterilized or have been free from menses for > 1 year.

- Male subject should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.
- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might interfere with the subject's participation for the full duration of the trial or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

Subjects who restart treatment will be retreated at the same dose and dose interval as when they last received pembrolizumab. Treatment will be administered for up to one additional year.

Visit requirements are outlined in Section 6.0 Trial Flow Chart.

Primary Completion:

The study will reach primary completion 24 months from the time the study opens to accrual.

Study Completion:

The study will reach study completion 36 months from the time the study opens to accrual.

4. TREATMENT PLAN

The treatment to be used in this trial is outlined below in Table 2.

Table 2. Trial Treatment

Arm	Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen / Treatment Period	Use
1	Pembrolizumab	200 mg flat dose	Q3 wks*	IV infusion	Day 1 of each 3-week cycle	Experimental
2	Pembrolizumab plus vismodegib (latter to be supplied as standard of care (SOC)	200 mg flat dose pembrolizumab	Q3 wks*	IV infusion	Day 1 of each 3-week cycle	Experimental
		150 mg vismodegib	Daily	Oral	Every day starting with Cycle 1, Day 1	Standard of Care
	Dose alterations for immune toxicities will be followed as per Merck guidelines.					

*until disease progression or intolerable toxicity.

Dose selection is as described above. In the case of an adverse event deemed related to the study drug that is Grade 3 or 4, study drug may be held for up to 6 weeks; if the subject had been deriving clinical benefit from the study agent, that is, stable, partial or complete response, the subject may be allowed to resume study drug after adverse event returns to Grade 1, with reduction in dosage by 50% or as recommended by the sponsor.

The rationale for selection of doses to be used in this trial is provided in Section 4.0 Background and Rationale.

Details on preparation and administration of pembrolizumab are provided in the Pharmacy Manual.

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Trial treatment may be

administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

Pembrolizumab 200 mg will be administered as a 30-minute IV infusion every 3 weeks. 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 (ie, infusion time is 30 minutes: -5 minute/+10 minute).

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

This is an open-label trial; therefore, the Sponsor, investigator and subject will know the treatment administered.

4.1 General Concomitant Medication and Supportive Care Guidelines

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

All 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.

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.

- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
- Intraarticular, inhaled, topical, and intralesional steroid treatments are allowed. A pulse steroid dose prior to and after imaging to prevent contrast allergy in patients with known allergy to contrast is allowed.

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

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

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

There are no rescue medications for this study. Supportive care is as outlined as follows. 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 and in greater detail in the ECI guidance document. 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 is instructed to follow the ECI reporting guidance but does not need to follow the treatment guidance (as outlined in the ECI guidance document). 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. Suggested conditional procedures, as appropriate, can be found in the ECI guidance document.

- **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 or 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** that persists greater than 3 days, administer oral corticosteroids.
  - For **Grade 3 or 4 diarrhea/colitis** that persists > 1 week, 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 or 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 or 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 to 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 or 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 to 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 to 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 3 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab.

Table 3. 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 (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDS • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5 hr (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: • Diphenhydramine 50 mg po (or equivalent dose of antihistamine). • Acetaminophen 500 to 1000 mg po (or equivalent dose of antipyretic).

Table 3. Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, 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.		

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm. 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 2 barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy.

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

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, 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 and to Merck without delay and within 24 hours to the Sponsor and within 2 working days to Merck if the outcome is a serious adverse experience (eg, 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. 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 and to Merck.

It is unknown whether pembrolizumab 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.

4.2 Criteria for Removal from Study

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 if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed radiographic disease progression

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

- Unacceptable adverse experiences
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 24 months of uninterrupted treatment with pembrolizumab or 35 administrations of study medication, whichever is later.

Note: 24 months of study medication is calculated from the date of first dose. Subjects who stop pembrolizumab after 24 months may be eligible for up to 1 year of additional study treatment if they progress after stopping study treatment provided they meet the requirements

- Administrative reasons

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). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each

subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 weeks with pembrolizumab and had at least two treatments with pembrolizumab beyond the date when the initial CR was declared. Subjects who then experience radiographic disease progression may be eligible for up to 1 year of additional treatment with pembrolizumab via the Second Course Phase at the discretion of the investigator if no cancer treatment was administered since the last dose of pembrolizumab, the subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open. Subjects will resume therapy at the same dose and schedule at the time of initial discontinuation.

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. **There are 2 or more responders in one arm**
   AND
   There are no responders in the other arm (after 10 patients have been enrolled in this latter arm).

In the event of Merck decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

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 7.2 Assessing and Recording 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 7.1.5.5. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.3.1) and then proceed to the Follow-Up Period of the study (described in Section 7.1.5.4).

4.3 Alternatives

All study subjects will discuss their treatment alternatives with their primary care physician or medical oncologist prior to enrollment in the study as well as with the investigator of this study.

5. STUDY AGENT INFORMATION

5.1 Study Agent Pembrolizumab

Clinical Supplies, as investigational pembrolizumab, will be provided by Merck as summarized in Table 4.

Table 4. Product Descriptions

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

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

5.2 Availability

Investigational pembrolizumab will be provided by Merck.

5.3 Study Agent Ordering

Investigational pembrolizumab will be requested from Merck by principal investigator and drug will be shipped to the Stanford Investigational Pharmacy, Attention: Martha Hamilton, PharmD.

5.4 Study Agent Accountability

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.

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

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

The clinical trial drug supply assigned to this study may not be used for any purpose other than that stated in the protocol.

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

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

6. DOSE MODIFICATIONS

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 4 below.

Table 5. Dose Modification Guidelines for Drug-Related Adverse Events

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject
Diarrhea / Colitis	2 to 3	Toxicity resolves to Grade 0 to 1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0 to 1	Toxicity does not resolve within 12 weeks of last dose.
	3 to 4	Permanently discontinue (see exception below)[1]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3 to 4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3 to 4 hyperglycemia associated with evidence of beta cell failure.	Resume pembrolizumab when patients are clinically and metabolically stable.
Hypophysitis	2 to 3	Toxicity resolves to Grade 0 to 1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hyperthyroidism	3	Toxicity resolves to Grade 0 to 1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism	2 to 4	Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted	Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted.
Infusion Reaction	3 to 4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0 to 1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3 to 4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0 to 1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3 to 4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[2]	3 or Severe	Toxicity resolves to Grade 0 to 1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue

Note: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event.

[1] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.

[2] Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0 to 1 within 12 weeks of the last dose.

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

Dose reductions are not allowed in this study.

7. ADVERSE EVENTS AND REPORTING PROCEDURES

7.1 Potential Adverse Events

Known or potential risks associated with pembrolizumab include immune mediated adverse reactions, including pneumonitis, diarrhea/colitis. Reported adverse reactions in 20% or greater of patients included fatigue, cough, nausea, pruritus, rash, decreased appetite constipation, arthralgia and diarrhea. Additional details of the adverse reactions are as follows:

Immune-Mediated Pneumonitis

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

Monitor patients for signs and symptoms of pneumonitis. Evaluate patients with suspected pneumonitis with radiographic imaging and administer corticosteroids for Grade 2 or greater pneumonitis. Withhold pembrolizumab for moderate (Grade 2) pneumonitis, and permanently discontinue pembrolizumab for severe (Grade 3) or life-threatening (Grade 4) pneumonitis *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)]*.

Immune-Mediated Colitis

Colitis (including microscopic colitis) occurred in 4 (1%) of 411 patients, including Grade 2 or 3 cases in 1 (0.2%) and 2 (0.5%) patients, respectively, receiving pembrolizumab in Trial 1. The median time to onset of colitis was 6.5 months (range 2.3 to .8). The median duration was 2.6 months (range 0.6 weeks to 3.6 months). All three patients with Grade 2 or 3 colitis were treated with high-dose corticosteroids (greater than or equal to 40 mg prednisone or equivalent per day) with a median initial dose of 70 mg/day of prednisone or equivalent; the median duration of initial treatment was 7 days (range 4 to 41), followed by a corticosteroid taper. One patient (0.2%) required permanent discontinuation of pembrolizumab due to colitis. All 4 patients with colitis experienced complete resolution of the event.

Monitor patients for signs and symptoms of colitis. Administer corticosteroids for Grade 2 or greater colitis. Withhold pembrolizumab for moderate (Grade 2) or severe (Grade 3) colitis, and permanently discontinue pembrolizumab for life-threatening (Grade 4) colitis *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)]*.

Immune-Mediated Hepatitis

Hepatitis (including autoimmune hepatitis) occurred in 2 (0.5%) of 411 patients, including a Grade 4 case in 1 (0.2%) patient, receiving pembrolizumab in Trial 1. The time to onset was 22 days for the case of Grade 4 hepatitis which lasted 1.1 months. The patient with Grade 4 hepatitis permanently discontinued pembrolizumab and was treated with high-dose (greater than

or equal to 40 mg prednisone or equivalent per day) systemic corticosteroids followed by a corticosteroid taper. Both patients with hepatitis experienced complete resolution of the event.

Monitor patients for changes in liver function. Administer corticosteroids for Grade 2 or greater hepatitis and, based on severity of liver enzyme elevations, withhold or discontinue pembrolizumab.

Immune-Mediated Hypophysitis

Hypophysitis occurred in 2 (0.5%) of 411 patients, consisting of one Grade 2 and one Grade 4 case (0.2% each), in patients receiving pembrolizumab in Trial 1. The time to onset was 1.7 months for the patient with Grade 4 hypophysitis and 1.3 months for the patient with Grade 2 hypophysitis. Both patients were treated with high-dose (greater than or equal to 40 mg prednisone or equivalent per day) corticosteroids followed by a corticosteroid taper and remained on a physiologic replacement dose.

Monitor for signs and symptoms of hypophysitis. Administer corticosteroids for Grade 2 or greater hypophysitis. Withhold pembrolizumab for moderate (Grade 2) hypophysitis, withhold or discontinue pembrolizumab for severe (Grade 3) hypophysitis, and permanently discontinue pembrolizumab for life- threatening (Grade 4) hypophysitis

Renal Failure and Immune-Mediated Nephritis

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

Monitor patients for changes in renal function. Administer corticosteroids for Grade 2 or greater nephritis. Withhold pembrolizumab for moderate (Grade 2) nephritis, and permanently discontinue pembrolizumab for severe (Grade 3), or life-threatening (Grade 4) nephritis

Immune-Mediated Hyperthyroidism and Hypothyroidism

Hyperthyroidism occurred in 5 (1.2%) of 411 patients, including Grade 2 or 3 cases in 2 (0.5%) and 1 (0.2%) patients, respectively, receiving pembrolizumab in Trial 1. The median time to onset was 1.5 months (range 0.5 to 2.1). The median duration was 2.8 months (range 0.9 to 6.1). One of two patients with Grade 2 and the one patient with Grade 3 hyperthyroidism required initial treatment with high-dose corticosteroids (greater than or equal to 40 mg prednisone or equivalent per day) followed by a corticosteroid taper. One patient (0.2%) required permanent discontinuation of pembrolizumab due to hyperthyroidism. All five patients with hyperthyroidism experienced complete resolution of the event.

Hypothyroidism occurred in 34 (8.3%) of 411 patients, including a Grade 3 case in 1 (0.2%) patient, receiving pembrolizumab in Trial 1. The median time to onset of hypothyroidism was 3.5 months (range 0.7 weeks to 19 months). All but two of the patients with hypothyroidism were treated with long-term thyroid hormone replacement therapy. The other two patients only

required short-term thyroid hormone replacement therapy. No patient received corticosteroids or discontinued pembrolizumab for management of hypothyroidism..

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.

Administer corticosteroids for Grade 3 or greater hyperthyroidism, withhold pembrolizumab for severe (Grade 3) hyperthyroidism, and permanently discontinue pembrolizumab for life-threatening (Grade 4) hyperthyroidism. Isolated hypothyroidism may be managed with replacement therapy without treatment interruption and without corticosteroids.

Other Immune-Mediated Adverse Reactions

Other clinically important immune-mediated adverse reactions can occur.

The following clinically significant, immune-mediated adverse reactions occurred in less than 1% of patients treated with pembrolizumab in Trial 1: exfoliative dermatitis, uveitis, arthritis, myositis, pancreatitis, hemolytic anemia, partial seizures arising in a patient with inflammatory foci in brain parenchyma, and adrenal insufficiency.

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

For suspected immune-mediated adverse reactions, ensure adequate evaluation to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, withhold pembrolizumab and administer corticosteroids. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Restart pembrolizumab if the adverse reaction remains at Grade 1 or less. Permanently discontinue pembrolizumab for any severe or Grade 3 immune-mediated adverse reaction that recurs and for any life-threatening immune-mediated adverse reaction

Embryofetal Toxicity

Based on its mechanism of action, pembrolizumab may cause fetal harm when administered to a pregnant woman. Animal models link the PD-1/PDL-1 signaling pathway with maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to a fetus.

Advise females of reproductive potential to use highly effective contraception during treatment with pembrolizumab and for 4 months after the last dose of KEYTRUDA

7.2 Adverse Event Reporting

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (ie, any clinically significant adverse change in

frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Merck's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Merck product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by Merck for human use.

Adverse events may occur during the course of the use of Merck product in clinical trials or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Adverse events may also occur in screened subjects during any pre-allocation baseline period as a result of a protocol-specified intervention, including washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Progression of the cancer under study is not considered an adverse event unless it is considered to be drug related by the investigator.

All adverse events will be recorded from the time the consent form is signed through 30 days following cessation of treatment and at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in Section 7.2.3.1.

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

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

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

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

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), including the pregnancy of a male subject's female partner 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 and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

A serious adverse event is any adverse event occurring at any dose or during any use of Merck's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose;
- Is another important medical event

Refer to Table 6 for additional details regarding each of the above criteria.

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 from the time the consent is signed through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety.

Non-serious Events of Clinical Interest will be forwarded to Merck Global Safety and will be handled in the same manner as SAEs.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Merck product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor and to Merck.

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-993-1220

A copy of all 15-Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc) at the time of submission. Additionally investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215-993-1220) at the time of submission to FDA.

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

Non-serious and serious adverse events must be recorded as such on the Adverse Event case report forms/worksheets. For this study, additional adverse events termed (events of clinical

interest) will include overdose of the study drug, elevation of liver enzymes greater than 3X ULN, an elevated total bilirubin lab value that is greater than or equal to 2X ULN and, at the same time, an alkaline phosphatase lab value that is less than 2X ULN.

Serious adverse events will be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-993-1220)

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

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

Table 6. Evaluating Adverse Events

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

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	• **Results in death**; or	
	• **Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	• **Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	• **Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); or	
	• **Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	• **Is a** new **cancer;** (that is not a condition of the study) **or**	
	• **Is an overdose** (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	• **Other important medical events** that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Merck product to be discontinued?	
Relationship to test drug	Did the Merck product cause the adverse event? The determination of the likelihood that the Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Merck product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was the Merck product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Merck product; or (3) the trial is a single-dose drug trial); or (4) Merck product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Merck product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Merck product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE MERCK PRODUCT, OR IF REEXPOSURE TO THE MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Merck product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Merck product relationship).**	
Yes, there is a reasonable possibility of Merck product relationship.	There is evidence of exposure to the Merck product. The temporal sequence of the AE onset relative to the administration of the Merck product is reasonable. The AE is more likely explained by the Merck product than by another cause.	
No, there is not a reasonable possibility Merck product relationship	Subject did not receive the Merck product OR temporal sequence of the AE onset relative to administration of the Merck product is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)	

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

8. CORRELATIVE/SPECIAL STUDIES

Archival specimens will be used when tumor is not accessible for biopsy prior to enrollment. Otherwise, tumor biopsy will be performed prior to enrollment as well as at the end of treatment time point.

8.1 Laboratory Correlative Studies

8.1.1 Immunohistochemistry will be performed by Merck.

8.1.1.1 Tissue will be collected by standard Keyes punch or shave biopsy technique as used in Dermatology clinic. In cases where tumor tissue is not accessible on the skin, archival specimens which are formalin fixed paraffin embedded will be obtained for correlative studies.

8.1.1.2 Specimens will be collected by the study coordinator or protocol director.

8.1.1.3 Specimens will be shipped in padded envelopes in plastic containers.

8.1.1.4 Merck will perform correlative studies except for the DNA and RNA studies. DNA and RNA studies will be performed at Stanford and at the Stanford Human Immune Monitoring Core to identify sequence changes that might predict tumor response.

8.1.1.5 Specimens will be coded by study name and number only prior to sending. The code will be kept in a locked cabinet accessible by research staff only at Stanford.

9. STUDY CALENDAR

Trial Period:	**Screening Phase**	**Treatment Cycles (if Arm 2, vismodegib or other FDA approved smoothened inhibitor will be given concurrently)** (One cycle is defined as 21 days)								**End of Treatment**	**Post-Treatment**
Treatment Cycle / Title	Screening (Visit 1)	1	2	3	4	5	6	7	8 plus	At time of Discontinuation	Follow-up 30 days post-discontinuation
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3		
Administrative Procedures											
Informed Consent	X *										
Inclusion/Exclusion Criteria	X	X									
Demographics and Medical History	X	X									
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X
Trial Treatment Administration		X	X	X	X	X	X	X	X		
Post-study anticancer therapy status											X
Survival Status **											X (and 90-day call)
Clinical Procedures/Assessments											
Review Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Physical Examination (full or targeted) ***	X	X	X	X	X	X	X	X	X	X	X
Vital Signs and Weight	X	X	X	X	X	X	X	X	X	X	X
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory											
Pregnancy Test – Urine or Serum β-HCG if female of childbearing potential	X	X								X	PRN
PT/INR and aPTT	X										
CBC with Differential	X	X	X	X	X	X	X	X	X	X	X
Comprehensive Serum Chemistry Panel	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X	X
T3, FT4 and TSH	X	X	X	X	X	X	X	X	X	X	X
Efficacy Measurements											
Tumor Imaging (within 28 days of Cycle 1, Day 1)	X				X (C4D1)			X (C7 D1)	See below	If not performed within 3 months of EOT visit	
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood											
Archival or Newly Obtained Tissue Collection	X				X, if accessible to biopsy					X, if accessible to biopsy	

Trial Period:	**Screening Phase**	**Treatment Cycles (if Arm 2, vismodegib or other FDA approved smoothened inhibitor will be given concurrently)** (One cycle is defined as 21 days)								**End of Treatment**	**Post-Treatment**
Treatment Cycle / Title	Screening (Visit 1)	1	2	3	4	5	6	7	8 plus	At time of Discontinuation	Follow-up 30 days post-discontinuation
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3		
Correlative Studies Blood Collection	X				X					X	

Note that post-treatment visits may occur every 30 days up until 90 days total as needed to follow resolution of adverse event.

Tumor biopsies to be collected at Cycle 4 and End of Treatment are based on investigator discretion and clinical judgement, timing is flexible based on tumor regression pattern(s).

Tumor imaging to be performed at Screening; Cycle 4; Cycle 7; and then every 3 cycles after as necessary for the duration of study treatment; at the discretion of the investigator, imaging frequency can by reduced by 50% if patient has stable disease for greater than 1 year

* Within 28 days of enrollment not required

** **Survival status clarification**: Participants who are followed by local oncologists and continue to receive pembrolizumab and/or vismodegib may be included for the purposes of overall survival analysis if documented by a progress note by the local oncologist or other physician, followed for a maximum of two years after enrollment

*** Full physical examination at screening constitutes of examination according to physician clinical judgement of at least 12 assessments including but not limited to: 1) general appearance; 2) conjunctiva; 3) eyelids; 4) ears; 5) scalp; 6) nose; 7) lips; 8) neck; 9) back; 10) chest; 11) abdomen; 12) arms; 13) legs; 14) genital area; 15) lymph nodes of the head and neck; 16) axillary lymph nodes; 17) inguinal lymph nodes; 18) epitrochlear lymph nodes; 19) popliteal lymph nodes; 20) nails; 21) lung auscultation; 22) heart auscultation; 23) dorsalis pedis pulses; 24) radial pulses; 25) patient's mood; 26) affect; 27) orientation to person/place/ time; 28) thyroid palpation and inspection. Targeted physical examination may be conducted after screening.

10. MEASUREMENTS

For clinicaltrials.gov and Stanford Clinical Trials Directory compliance

10.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE version 4.0 (see Section 11.2). Toxicities will be characterized in terms regarding seriousness; causality; toxicity grading; and action taken with regard to trial treatment.

For subjects receiving treatment with pembrolizumab all AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (termed immune-related adverse events, or irAEs).

Please refer to Section 7.2 for detailed information regarding the assessment and recording of AEs.

10.1.2 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed during screening,

10.1.3 Directed Physical Exam

For cycles that do not require a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

10.1.4 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 6.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

10.1.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 11.1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

10.1.6 Tumor Imaging and Assessment of Disease

All participants will be imaged by CT or MRI scanning according to the study calendar. In cases where the disease is superficial and the investigator deems clinical examination is adequate to follow the NMSC, no imaging will be performed.

10.1.7 Tumor Tissue Collection

Archival specimens will be used when tumor is not accessible for biopsy prior to enrollment. Otherwise, tumor biopsy will be performed prior to enrollment, while on treatment (at Cycle 4), as well as at the end of treatment time point. However, based on investigator discretion and clinical judgement, the required biopsy time point at Cycle 4 can be completed prior to Cycle 4 depending upon tumor regression pattern(s) during the first few treatments.

10.1.8 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 7.

Table 7. Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	Total thriiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	Free tyroxine (T4)
Absolute Lymphocyte Count	*(CO_2 or biocarbonate)*	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Uric Acid		PK
	Calcium		
	Chloride		Blood for correlative studies
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		

† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.

‡ If considered standard of care in your region.

Laboratory tests for screening or entry into the Second Course Phase should be performed within 10 days prior to the first dose of treatment if they are not to be repeated at Cycle 1 Day 1. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment

10.1.9 Pharmacokinetic/Pharmacodynamic Evaluations

10.1.9.1 Blood Collection for Serum Pembrolizumab

Sample collection, storage and shipment instructions for serum samples will be provided in the Laboratory Manual.

There is no PK sampling in this study.

10.1.9.2 Blood Collection for Anti-Pembrolizumab Antibodies

Sample collection, storage and shipment instructions for blood samples will be provided in the Laboratory Manual.

10.2 Primary and Secondary Outcome measures

RECIST version 1.1* will be used in this study for assessment of tumor response. While either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study. Where the target tumor is visible to clinical inspection, high quality color photographs will be taken with a ruler in the plane of tumor, and the longest diameter will be assessed and recorded as the measurement.

* As published in the European Journal of Cancer: EA Eisenhauer, P Therasse, J Bogaerts, *et al*. "New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1)." *Eur J Cancer*. Jan 2009;45(2):228-247.

10.2.1 Relevant Subset

Only participants who return after Cycle 1, Day 1 will be analyzed. We anticipate 24 study subjects will be analyzable.

10.2.2 Measurement Definition

Give a detailed definition of the quantity or categorization to be measured. For example:

- Overall response rate will be calculated by dividing the number of subjects with partial or complete response by RECIST v1.1 divided by the total number of analyzable subjects.

10.2.3 Measurement Methods

Response will be measured by RECIST v1.1. If tumor is visible on clinical inspection, then the tumor will be measured with calipers in centimeters. If the tumor is not visible on clinical inspection then either CT scan or MRI will be used, and the longest diameters will be ascertained for the target lesion(s) per RECIST v1.1.

10.2.4 Measurement Time Points

Efficacy outcome assessments will be at after 9 and 18 weeks of treatment. This represents 3 and 6 cycles of treatment, with a cycle considered to be 3 weeks (21 days).

Safety assessments will be continuous with follow-up for 30 days after last dose or until discontinuation or adverse event.

10.2.5 Response Review

Simultaneous review of the patients' files and radiological images will be performed. However, we do not have resources for independent review of our data besides the Stanford Data Safety Monitoring Committee.

10.3 Secondary Outcome

Adverse event number and grade will be recorded for both arms of the study and reported.

Biomarker levels will be recorded using both qualitative and quantitative measures.

11. REGULATORY CONSIDERATIONS

11.1 Institutional Review of Protocol

The protocol, the proposed informed consent and all forms of participant information related to the study (eg, advertisements used to recruit participants) will be reviewed and approved by the Stanford IRB and Stanford Cancer Institute Scientific Review Committee (SRC). Any changes made to the protocol will be submitted as a modification and will be approved by the IRB prior to implementation. The Protocol Director will disseminate the protocol amendment information to all participating investigators.

11.2 Data and Safety Monitoring Plan

The Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) will be the monitoring entity for this study. The DSMC will audit study-related activities to determine whether the study has been conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). This may include review of the following types of documents participating in the study: regulatory binders, case report forms, eligibility checklists, and source documents. In addition, the DSMC will regularly review serious adverse events and protocol deviations associated with the research to ensure the protection of human subjects. 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 needed.

11.3 Data Management Plan

Case Report Forms (CRFs) are printed or electronic documents designed to record all protocol-related information on each trial participant. CRFs should summarize the clinical findings and observations necessary to ensure safety of participants on the study, and to document the study outcomes. CRFs are required by the SRC for all Interventional studies. CRF design and creation must be completed prior to enrollment of the first participant. Describe your plan for developing CRFs, stating what medium will be used, (eg. OnCore, REDCap, paper documents) and where the CRFs will be stored. For electronic data capture using OnCore, contact the OnCore Team at CCTO-OnCore@stanford.edu; for REDCap, contact redcap-help@lists.stanford.edu.

The Protocol Director, or his/her designee, will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document treatment outcomes for data analysis. Case report forms will be developed using the database system and will be maintained by the study coordinator. CRFs will be kept in a locked office, only accessible to the research team.

12. STATISTICAL CONSIDERATIONS

12.1 Statistical Design

Open-label; non-comparative; 2-arm study of efficacy and safety of pembrolizumab in unresectable and/or metastatic basal cell carcinomas.

12.1.1 Randomization

All subjects will receive the treatment. There will be no randomization.

12.2 Interim analyses

The study will terminate if all of the first 10 patients who enroll show progressive disease at the end of Cycle 3.

Interim analysis will be performed after 13 patients are enrolled.

12.3 Descriptive Statistics and Exploratory Data Analysis

Descriptive statistics will be used to summarize the participants in each arm, including mean and median age, sex, prior treatments, duration on study drug, and location of tumor.

12.4 Primary Analysis

- Primary endpoint 1: To assess the overall response rate (ORR) of unresectable or metastatic BCC patients to pembrolizumab, (percentage of all evaluable patients with partial or complete response after 9 and 18 weeks of treatment including pembrolizumab and pembrolizumab plus vismodegib groups)

12.4.1 Analysis Population

Only individuals who enroll and return for one additional study visit will be analyzed. Non-adherence will be noted in the patient charts, and those who are non-adherent due to toxicity will be recorded and noted as such. They will be included in the analysis population with the new baseline being time of study drug restart if more than 1 month has elapsed since study drug pause.

12.4.2. Analysis Plan

Overall response rate of the 2 arms will be calculated.

12.5 Secondary Analysis

- Secondary endpoint 1: To assess the ORRs of unresectable or metastatic BCC patients to A) pembrolizumab monotherapy (separately and not directly compared statistically), and B) pembrolizumab and vismodegib, as percentage of patients with partial or complete response after 9 and 18 weeks of treatment).
- Secondary endpoint 2: To assess the safety and tolerability of pembrolizumab (both monotherapy or combination therapy) for unresectable or metastatic basal cell carcinoma, assessed as the percentage of treated patients experiencing any adverse events, or related adverse events Grade 3 or higher, in each of the two study arms

- Secondary endpoint 3: To assess the duration of response after pembrolizumab as monotherapy and in combination with vismodegib, assessed as the median value after 9 and 18 weeks of treatment.
- Exploratory endpoint 1: To assess the effect of pembrolizumab (both monotherapy and together with vismodegib) on the level of PDL1 and CD8 density by immunostaining
- Exploratory endpoint 2: To assess if pembrolizumab may improve overall survival (OS) in unresectable or metastatic BCC patients (both as monotherapy and combination therapy)

12.5.1 Analysis Population

Only individuals who enroll, take at least one dose of study drug and return for one additional study visit will be analyzed. Non-adherence will be noted in the patient charts, and those who are non-adherent due to toxicity will be recorded and noted as such. They will be included in the analysis population with the new baseline being time of study drug restart if more than 1 month has elapsed since study drug pause.

12.5.2. Analysis Plan

Endpoints will be tallied for the events or biomarkers of interest and compared between the arms.

Specifically, outcomes to be reported to ClinicalTrials.gov upon completion of this study include

1 Primary: ORR on pembrolizumab monotherapy

Measure title: Overall Response to pembrolizumab for all evaluable patients on the study, regardless of monotherapy or with vismodegib

Measure description: Percentage of patients with partial or complete response after pembrolizumab

Time frame 6 cycles (18 weeks), also 3 cycles (9 weeks)

Safety issue: No

Measure summary: Overall Response Rate to be calculated as the ratio of patients with CR or PR as a percentage of patients evaluable for OR

Population: all patients who enroll and take at least one dose of study agent and have at least one follow up evaluation timepoint

2 Secondary: ORR on pembrolizumab plus vismodegib combination therapy

Measure title: Overall Response on A) pembrolizumab monotherapy and B) pembrolizumab plus vismodegib therapy in noncomparative fashion

Measure description: Percentage of patients with partial or complete response after pembrolizumab plus vismodegib combination therapy or pembrolizumba monotherapy but not directly compared

Time frame: after 3 and 6 cycles

Safety issue: No

Measure summary: Overall Response Rate to be calculated as the ratio of patients with CR or PR as a percentage of patients evaluable for OR for pembrolizumab and vismodegib or pembrolizumab monotherapy as separate groups

Population: all patients who enroll and take at least one dose of study agents, and have at least one follow up evaluation timepoint

3 Secondary: safety and tolerability

Measure title: safety and tolerability

Measure description: Percentage of patients experiencing with adverse events any adverse events, or related adverse events Grade 3 or higher, in each of the two study arms (including type and grade)

Time frame: after 3 and 6 cycles

Safety issue: Yes

Measure summary: Percentage of treated patients with adverse events of any grade, and percentage of patients with related adverse events Grade 3 or higher after pembrolizumab monotherapy or pembrolizumab in combination with vismodegib

Population: patients who enroll, take at least one dose of study agent and have at least one follow-up evaluation

4 Secondary: duration of response

Measure title: median duration of response

Measure description: time from first partial or complete response to disease progression by RECIST v1.1

Time frame: 2 years

Safety issue: No

Measure summary: Median duration of response (DOR) in months, with 1st and 3rd quartiles, by cohort, ie, for all evaluable patients, as well as divided into pembrolizumab monotherapy or pembrolizumab in combination with vismodegib

Population: patients who enroll, take at least one dose of study agent and have at least one follow up evaluation

5A Secondary: biomarkers before and after treatment

Measure title: level of PDL1 and CD8 by immunostaining on pembrolizumab either monotherapy or together with vismodegib

Measure description: percentage of PDL1 positive tumor cells, and percentage of CD8 positive tumor and immune infiltrate

Time frame: after cycle 3

Safety issue: No

Measure summary: percentage of total tumor cells, percentage of total tumor immune infiltrate

Population: patients who enroll, take at least one dose of study agent and have at least one follow up evaluation

5B Secondary: biomarkers before and after treatment for all evaluable patients

Measure title: level of PDL1 and CD8 by immunostaining for all evaluable patients

Measure description: percentage of PDL1 positive tumor cells, and percentage of CD8 positive tumor and immune infiltrate

Time frame: after cycle 3

Safety issue: No

Measure summary: percentage of total tumor cells, percentage of total tumor immune infiltrate

Population: patients who enroll, take at least one dose of study agents and have at least one follow up evaluation

6A Secondary: overall survival

Measure title: overall survival of all evaluable patients

Measure description: number of months from study enrollment to last study visit

Time frame: 2 years

Safety issue: No

Measure summary: OS will be reported in months and Kaplan-Meier median will be reported

Population: patients who enroll, take at least one dose of study agent and have at least one follow up evaluation

6B Secondary: overall survival

Measure title: overall survival of all evaluable patients

Measure description: number of months from study enrollment to last study visit

Time frame: 2 years

Safety issue: No

Measure summary: OS will be reported in months and Kaplan-Meier median will be reported

Population: patients who enroll, take at least one dose of study agents and have at least one follow up evaluation

12.6 Sample Size

As this is an exploratory non-comparative study, statistics between the two groups was not performed. However, for practical purposes, prospective statistical design was based on a minimum ORR of 10% for all evaluable patients, defined as the minimum clinically meaningful rate given potential risks of pembrolizumab exposure. Based on an estimated ORR of 30%, with two-sided alpha=0.05 ($p<0.05$) and power=0.84, the pre-determined sample size was 26 evaluable patients, with pembrolizumab monotherapy group and pembrolizumab plus vismodegib group included within this number.

We plan to enroll 13 subjects per arm for a total of 26 participants. However, the study enrollment will discontinue if the primary endpoint is met at interim analysis.

12.6.1 Accrual estimates

Estimates are based on prior studies. We anticipate 13 patients per year will enroll. If accrual falls short, we will reach out to community physicians for referrals through word of mouth or paper advertisements.

12.6.2 Sample size justification

Consultation with Alex McMillan, PhD and Shufeng Li, MS, both biostatisticians led to the following:

This is a proof-of-concept study, phase 1b. Because advanced basal cells carcinoma is a rare disease, this is a non-comparative study. The primary and secondary endpoints are descriptive and the arms will not be compared. The data from this study will be used to power future multi-center studies.

12.6.3 Effect size justification

This study is exploratory and does not include effect size analysis.

12.7 Criteria for future studies

Success will be defined as 20% response rate for pembrolizumab monotherapy arm. Currently, for patients with advanced BCC refractory or resistant to Smoothened monotherapy, there is no good treatment and all patients experience disease progression.

13. REFERENCES

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Wolfle SJ, *et al.* (2011) PD-L1 expression for tolerogenic APCs is controlled by STAT-3. *Eur J Immunol* 41(2): 413-24.

APPENDICES

APPENDIX A**: Participant Eligibility Checklist**

A Participant Eligibility Checklist must be completed in its entirety for each subject prior to registration. The completed, signed, and dated checklist must be retained in the patient's study file and the study's Regulatory Binder.

The study coordinator, treating physician and an independent reviewer must verify that the participant's eligibility is accurate, complete, and legible in source records. A description of the eligibility verification process should be included in the EPIC or other Electronic Medical Record progress note.

Protocol Title:	A phase 1b open-label study of pembrolizumab for unresectable or metastatic basal cell carcinoma
Protocol Number:	IRB-34925 / SKIN0031
Principal Investigator:	Anne Lynn S Chang, MD

II. Subject Information:

Subject Name/ID:
Gender: ☐ Male ☐ Female

III. Study Information:

SRC Approved ☐ IRB Approved ☒ Contract signed ☐

IV. Inclusion/Exclusion Criteria

Inclusion Criteria (From IRB-approved protocol)	**Yes**	**No**	**Supporting Documentation***
1. Be willing and able to provide written informed consent/assent for the trial. Consent may be obtained by LAR according to the protocol.	☐	☐	
2. Have a histologically-proven BCC in which curative resection is unlikely without significant morbidity, or have nodal or distantly metastatic disease which has progressed on smoothened inhibitor monotherapy (ARM 1) or has undergone partial response or stable disease on smoothened inhibitor monotherapy (ARM 2). Individuals who are intolerant or have a medical contra-indication to smoothened inhibitor may be enrolled into ARM 1.	☐	☐	
3. Be ≥ 18 years of age on day of informed consent signing .	☐	☐	
4. Have measurable disease based on RECIST 1.1.	☐	☐	
5. Be willing to provide tissue from a newly obtained core or excisional biopsy of a tumor lesion. *Newly-obtained is defined as a specimen obtained up to 6 weeks (42 days) prior to initiation of treatment on Day 1. Subjects for whom newly-obtained samples cannot be provided (eg, inaccessible or subject safety concern) may submit an archived specimen. .*	☐	☐	

Inclusion Criteria (From IRB-approved protocol)	**Yes**	**No**	**Supporting Documentation***
6. Have a performance status of 0 or 1 on the ECOG Performance Scale.	☐	☐	
7. Demonstrate adequate organ function as defined in Table 3 (repeated below); all screening labs should be performed within 10 days of treatment initiation.	☐	☐	
8. Female subject of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the 1st dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.	☐	☐	
9. Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Section 5.7.2). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.	☐	☐	
10. Male subjects should agree to use an adequate method of contraception starting with the 1st dose of study therapy through 120 days after the last dose of study therapy.	☐	☐	
11. Female is not breastfeeding, is postmenopausal or surgically sterile; demonstrates non-pregnant state, and agrees to use 2 acceptable methods of birth control throughout the trial, until 120 days after the last dose of treatment	☐	☐	
12. Male with female partner of childbearing potential agrees to use adequate method of contraception throughout study, until 120 days after last dose of treatment or last blood draw.	☐	☐	

Table 1. Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥ 1,500/mcL
Platelets	≥ 100,000/mcL
Hemoglobin	≥ 9 g/dL or ≥ 5.6 mmol/L without transfusion or EPO dependency (within 7 days of assessment)
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤ 1.5 x upper limit of normal (ULN) **OR** ≥ 60 mL/min for subject with creatinine levels > 1.5 x institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 x ULN **OR** Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 x ULN **OR** ≤ 5 x ULN for subjects with liver metastases
Albumin	≥ 2.5 mg/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤ 1.5 x ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	≤ 1.5 X ULN unless subject is receiving anticoagulant therapy, as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a] Creatinine clearance should be calculated per institutional standard.	

Exclusion Criteria (From IRB-approved protocol)	**Yes**	**No**	**Supporting Documentation***
1. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the 1st dose of treatment.	☐	☐	

Exclusion Criteria (From IRB-approved protocol)	**Yes**	**No**	**Supporting Documentation***
2. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the 1st dose of trial treatment. Exceptions include topical, intralesional intra-articular and inhaled steroids. A pulse steroid dose prior to and after imaging to prevent contrast allergy in patients with known allergy to contrast is allowed.	☐	☐	
3. Has a known history of active TB (Bacillus Tuberculosis)	☐	☐	
4. Hypersensitivity to pembrolizumab or any of its excipients.	☐	☐	
5. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to Study Day 1 or who has not recovered (ie, ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.	☐	☐	
6. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to Study Day 1 or who has not recovered (ie, ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent. a. Note: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study. b. Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.	☐	☐	
7. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.	☐	☐	
8. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least 4 weeks prior to the 1st dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.	☐	☐	
9. Has active autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc) is not considered a form of systemic treatment.	☐	☐	

Exclusion Criteria (From IRB-approved protocol)	**Yes**	**No**	**Supporting Documentation***
10. Has known history of, or any evidence of active, non-infectious pneumonitis.	☐	☐	
11. Has an active infection requiring systemic therapy.	☐	☐	
12. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.	☐	☐	
13. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.	☐	☐	
14. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.	☐	☐	
15. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.	☐	☐	
16. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1-2 antibodies).	☐	☐	
17. Has known active Hepatitis B (eg, HBsAg reactive) or Hepatitis C (eg, HCV RNA [qualitative] is detected)	☐	☐	
18. Has received a live vaccine within 30 days of planned start of study therapy.	☐	☐	

*****All subject files must include supporting documentation to confirm subject eligibility. The method of confirmation can include, but is not limited to, laboratory test results, radiology test results, subject self-report, and medical record review.

IV. Statement of Eligibility

By signing this form of this trial I verify that this subject is [☐ **eligible** / ☐ **ineligible**] for participation in the study. This study is approved by the Stanford Cancer Institute Scientific Review Committee, the Stanford IRB, and has finalized financial and contractual agreements as required by Stanford School of Medicine's Research Management Group.

Treating Physician Signature:	Date:
Printed Name:	

Secondary Reviewer Signature:	Date:
Printed Name:	

Study Coordinator Signature:	Date:
Printed Name:	

APPENDIX B: ECOG Performance Status

Grade	Description
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 (eg, 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.

* As published in *Am J Clin Oncol*: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. "Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group." *Am J Clin Oncol*. 1982;5:649-655. The Eastern Cooperative Oncology Group, Robert Comis, MD, Group Chair.

APPENDIX C: Common Terminology Criteria for Adverse Events v4.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)