SWOG CANCER RESEARCH NETWORK

Version Date: October 15, 2021

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS; CTSU

FROM: SWOG Operations Office (email: protocols@swog.org)

RE: **S1607**, "A Phase II Study of Combining Talimogene Laherparpvec (T-VEC) (NSC-785349) and Pembrolizumab (MK-3475) (NSC-776864) in Patients with Advanced Melanoma Who Have Progressed on Anti-PD1/L1 Based Therapy." Study Chairs: Drs. S. Hu-Lieskovan and A. Ribas

REVISION #10

Study Chair: Siwen Hu-Lieskovan, M.D., Ph.D.
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Action Codes
(✓) Expedited review allowed
(✓) Patients Must be Informed*
(✓) Formal Re-Consent Required*
(✓) Verbal notification allowed (in some cases, see below)
(✓) Consent Must Be Amended*

* See "Patient Notification and Use of Consent Addendum" and "Regulatory Considerations" instructions below.

Key Updates
(✓) Informed Consent changes
(✓) Other: pembrolizumab drug section

Sites using the CIRB as their IRB of record: The protocol and/or informed consent form changes have been approved by the CIRB and must be activated within 30 days of the CIRB posting of this notice.

Sites not using the NCI CIRB: Per CTMB Guidelines, the protocol updates and/or informed consent changes must be approved by local IRBs within 90 days of distribution of this notice.

REVISION #10

The above referenced study has been revised with the following changes in response to the Request for Rapid Amendment (RRA) for Pembrolizumab (MK3475) received on October 4, 2021 from Elad Sharon, M.D. (sharone@mail.nih.gov), Jeffrey Moscow, M.D. (jeffrey.moscow@nih.gov), and Meg Mooney, M.D. (mooneym@ctep.nci.nih.gov).. The associated Action Letter is attached.

Protocol Changes

1. The version date has been updated.

2. Section 3.1c: Pembrolizumab CAEPR (Version 2.6, July 15, 2021) has been updated as follows:

- Added New Risk:
  - Rare but Serious: Hepatobiliary disorders - Other (sclerosing cholangitis)
- Decrease in Risk Attribution:
  - Changed to Rare but Serious from Less Likely: Blood and lymphatic system disorders - Other (immune thrombocytopenic purpura)

- Provided Further Clarification:
    - Thrombotic thrombocytopenic purpura is now reported as Blood and lymphatic system disorders - Other (immune thrombocytopenic purpura).

Model Consent Form Changes

1. The version date has been updated.

2. Page 6-8: Under the heading "Risk Profile for pembrolizumab", the list of pembrolizumab risks has been updated as follows:

   Added New Risk:
   a. Rare: **Swelling of the gallbladder**

Patient Notification and use of Consent Addendum:

Please note that the information provided below regarding patient notification and amendments to local consent forms reflects SWOG's minimum requirements. Sites should refer to the policies/procedures of the IRB of record to determine whether they have any more stringent requirements.

SWOG has determined that the changes above that are **bolded** may affect a patient's willingness to participate in the study; therefore, SWOG requires that patients be notified of these changes.

Who must be informed?

- All patients currently on study treatment with pembrolizumab.

How must patients be notified?

- Notification must take place either via the attached Consent Addendum or via amended consent form by next study visit. After the change has been discussed with the patient, the patient must sign and date either the Consent Addendum or the 10/15/21 version of the consent form.

What is the notification deadline and process?

- Patients must be notified by their next scheduled visit or within 90 days after CTSU distribution of this revision, whichever is sooner.
- Sites using the NCI CIRB as their IRB of record: CIRB has approved the attached Consent Addendum; therefore, the Consent Addendum may be utilized immediately to notify patients of these changes.
- Sites not using the NCI CIRB as their IRB of record: If local IRB approval of the Consent Addendum is required before sites may utilize it, the site must still notify patients verbally prior to the notification deadline and notification must be documented in the patient chart. The site must then obtain patient signature on the Consent Addendum or updated consent form once the addendum and/or revised consent is locally approved.

Regulatory Considerations:

Do local consent forms need to be updated?

- It depends. If your site will utilize the updated consent form for notification and formal reconsent then local consent forms must be updated. If your site will not utilize updated consent form for notification and formal reconsent then local consent forms need not be updated.

The updated protocol and model informed consent can be accessed from the CTSU website (www.ctsu.org). Please discard any previous versions of the documents and replace with the updated versions. Please contact melanomaquestion@crab.org or 206/652-2267 with any questions.

This study has been reviewed and approved by the NCI's Central Institutional Review Board (CIRB).

This memorandum serves to notify the NCI and SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Jia Chen – UCLA
Austin Vega-Crespo – UCLA

Informed Consent Addendum Model for S1607

S1607, "Study Title for Study Participants: Testing the combination of talimogene laherparepvec and pembrolizumab in patients with advanced melanoma who have progressed on anti-PD-1/L1 therapy

The following information should be read as an update to the original Consent form that you read and signed at the beginning of the study. Unless specifically stated below, all information contained in that original Consent Form is still true and remains in effect. Your participation continues to be voluntary. You may refuse to participate, or may withdraw your consent to participate at any time, and for any reason, without jeopardizing your future care at this institution or your relationship with your study doctor.

New or additional information

The following new risk has been identified with the Pembrolizumab (MK-3475) updates:

Added New Risk:

1) **Rare: Swelling of the gallbladder**

Patient Signature and Date

By signing this form, I acknowledge that I have read the information above or had it read to me. I have discussed it with a member of the study team and my questions have been answered. I understand that I will be given a copy of this form.

Participant's signature (or legally authorized representative) _____

Date of signature_____

Signature of person(s) conducting the informed consent discussion_____

Date of signature _____

PRIVILEGED COMMUNICATION
FOR INVESTIGATIONAL USE ONLY

SWOG

A PHASE II STUDY OF COMBINING TALIMOGENE LAHERPAREPVEC (T-VEC) (NSC-785349) AND PEMBROLIZUMAB (MK-3475) (NSC-776864) IN PATIENTS WITH ADVANCED MELANOMA WHO HAVE PROGRESSED ON ANTI-PD1/L1 BASED THERAPY

NCT#02965716

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AGENTS:

NCI Supplied Investigational Agents:
Pembrolizumab (MK-3475)
(NSC-776864)

Talimogene Laherparepvec (T-VEC)
(NSC-785349)
IND Sponsor: DCTD, NCI –

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NRG/NRG Oncology
SWOG/SWOG

TABLE OF CONTENTS

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	**For patient enrollments:**	**Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA19103 Fax: 215-569-0206 Email: CTSURegulatory@ctsu.coccg.org For more information, call the CTSU Help Desk at 888-823-5923 or the Regulatory Help Desk at 866-651-CTSU.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions. Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions. Other Tools and Reports: Institutions participating through the CTSU continue to have access to other tools and reports available on the SWOG Workbench. Access this by using your active CTEP-IAM userid and password at the following url: https://crawb.crab.org/TXWB/ctsulogon.aspx
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.		
For patient eligibility questions contact the SWOG Data Operations Center by phone or email: 206-652-2267 melanomaquestion@crab.org **For treatment or toxicity related questions** contact the Study PI of the Coordinating Group.		
For questions unrelated to patient eligibility, treatment, or data submission contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line: 888-823-5923 ctsucontact@westat.com All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Web site is located at https://www.ctsu.org		

SCHEMA

Patients with advanced/metastatic melanoma who have progressed on anti-PD1/L1 therapy prior to registration.

↓

REGISTRATION

↓

Scan/Skin Exam
Biopsy and blood draw*
Archival tumor (prior to anti-PD1/L1), Optional but strongly recommended

↓

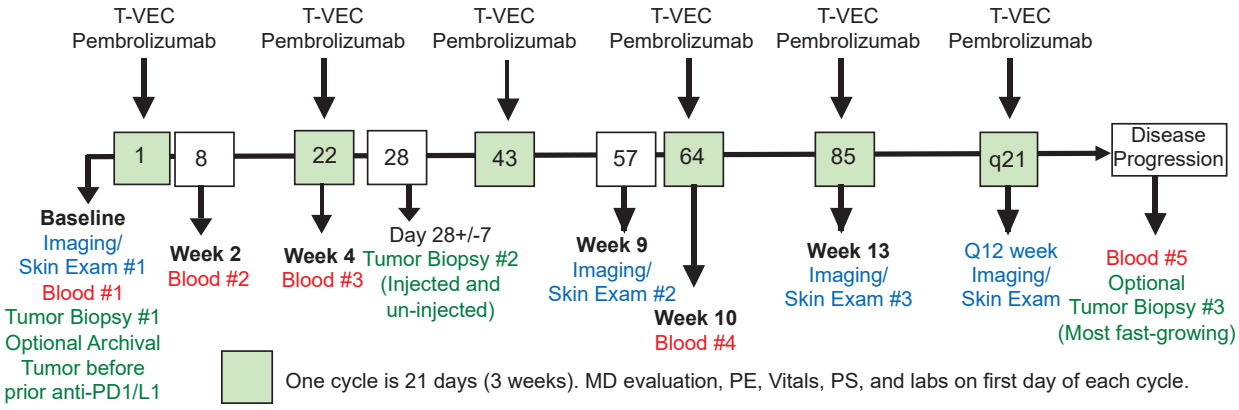
Continuous talimogene laherparepvec (T-VEC) + pembrolizumab (MK-3475)
(Scan/Skin Exam at Week 9, 13 and then every 12 weeks)
(Blood draw at Week 2, 4 and 10*)
(Biopsy at D28*, both injected and un-injected)

↓

Progression
(Blood draw and optional biopsy*)

↓

Off Treatment



* See Section 15.1.

1.0 OBJECTIVES

This study will enroll two separate cohorts (see Section 6.0) to assess the efficacy of talimogene laherparepvec (T-VEC) in combination with pembrolizumab (MK-3475). Each cohort will be analyzed independently.

1.1 Primary Objective(s)

To evaluate the objective response rate (confirmed complete and partial responses) of treatment with talimogene laherparepvec (T-VEC) in combination with pembrolizumab (MK-3475) following progression on prior anti-PD-1 or anti-PD-L1 therapy alone or in combination with other agents different from talimogene laherparepvec (T-VEC).

1.2 Secondary Objective(s)

a. To estimate the durable response rate (as defined in Section 10.7)

b. To estimate the objective response rate (ORR) defined as confirmed and unconfirmed, complete and partial responses in the injected lesions.

c. To estimate the ORR in the non-visceral, non-injected lesions.

d. To estimate the ORR in the visceral lesions (Cohort A).

e. To estimate the median progression-free survival (PFS).

f. To estimate the median overall survival (OS).

g. To evaluate the toxicity of the regimen.

1.3 Translational Objectives

a. To evaluate whether adding talimogene laherparepvec (T-VEC) to PD1 blockade can increase T-cell infiltration into tumors and whether change in T-cell infiltration is associated with response.

b. To evaluate whether adding talimogene laherparepvec (T-VEC) to PD1 blockade can increase TCR clonality in tumors and in peripheral blood and whether increased TCR clonality is associated with response.

c. To evaluate whether intra-tumoral injection of talimogene laherparepvec (T-VEC) can improve the tumor immune microenvironment.

d. To evaluate whether tumor mutational load, mutations in the IFN pathway, and circulating tumor DNA profile are associated with response to talimogene laherparepvec (T-VEC) plus pembrolizumab (MK-3475) therapy in the anti-PD1/L1 therapy refractory melanoma patients.

2.0 BACKGROUND

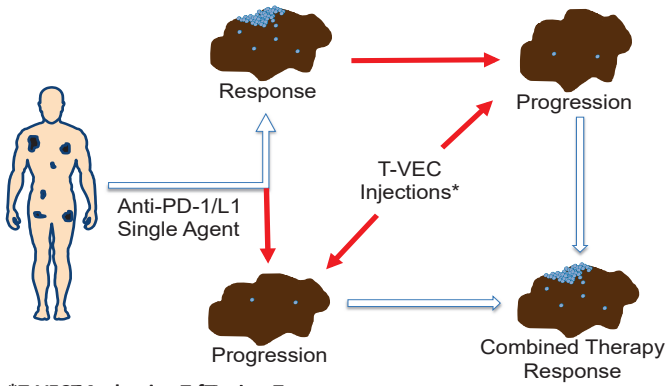
2.1 Overview

The programmed cell death 1 (PD-1) pathway represents a major immune checkpoint, which may be hijacked by tumor cells to overcome active T-cell immune surveillance. *(1,2,3)* The ligands for PD-1 (PD-L1 and PD-L2) can be constitutively expressed or can be induced on the surface of cancer cells in response to interferons produced by tumor-infiltrating lymphocytes, which provides a mechanism for the cancer cells to avoid immune surveillance. *(4)* Preclinical data have shown that PD-1 and/or PD-L1 blockade using monoclonal antibodies enhances tumor-specific T-cell activation, T-cell infiltration into the tumors, cytokine production, anti-tumor effector function, and clearance of tumor cells by the immune system. PD-1 therapy also modulates the level of interleukin-2 (IL-2), tumor necrosis factor alpha (TNFα), interferon gamma (IFNγ), and other cytokines in the tumor microenvironment.

Pembrolizumab (MK-3475) was the first anti-PD-1 antibody approved by FDA for advanced melanoma patients. *(5)* Studies have indicated that tumor regression following therapeutic PD-1 blockade requires 1) pre-existing CD8+ T-cells that are 2) negatively regulated by PD-1/PD-L1-mediated adaptive immune resistance. *(6)* Without these two requirements PD-1 blockade therapy is unlikely effective

Talimogene laherparepvec (T-VEC, formerly known as OncoVEXGM-CSF) is an oncolytic virus based on a modified herpes simplex virus type-1 (HSV-1). Itis designed to selectively replicate in tumor tissue and to stimulate local and systemic antitumor immune response (Figure 1). Intralesional administration of talimogene laherparepvec (T-VEC) results in oncolysis of tumor cells and local release of progeny virus as well as of tumor cell antigens. Viral pathogens are strong inducers of interferon responses, and their intratumoral injection results in a change in the tumor microenvironment that is more permissive to a T-cell response. Furthermore, GM-CSF, the product of the viral transgene, is also produced locally to recruit and stimulate antigen-presenting cells. Overall, this strategy is expected to result in the destruction of injected tumors via oncolysis and also uninjected sites of disease (including micro-metastases) via a systemic antitumor immune response.

Figure 1: Proposed mechanism of action of T-VEC.



*T-VEC Mechanism of Action:

1. T-VEC viruses only replicate in the tumor cells, causing tumor cell lyses, releasing more viruses and tumor antigen, causing local inflammation.
2. The viral construct is engineered to produce GM-CSF, attracts dendritic cells to process and present tumor antigen to T cells.
3. Interferon released by inflammatory cells can induce PD-L1 expression in the tumors, serving the rationale to combine T-VEC with PD1/L1 blockade

Talimogene laherparepvec (T-VEC) has been tested for efficacy in a variety of in vitro (cell line) and in vivo murine tumor models and has been shown to eradicate tumors or substantially inhibit their growth at doses comparable to those used in clinical studies. Nine clinical studies have been or are being conducted in several advanced tumor types (melanoma, squamous cell cancer of the head and neck [SCCHN], and pancreatic cancer),

with a total of 427 subjects treated with talimogene laherparepvec (T-VEC). Results of the pivotal Phase III trial (OPTiM) in melanoma have shown that talimogene laherparepvec (T-VEC) treatment as monotherapy results in durable responses (at least 6 months of continuous response) and objective responses in 16% and 26% of subjects with regional or distant metastases and limited visceral involvement, as compared to 2% and 5.7% in patients treated with GM-CSF. (7) The treatment was well tolerated with adverse events primarily including flu-like symptoms and injection site reactions. A Phase Ib/II study of ipilimumab with or without talimogene laherparepvec (T-VEC) in Stage IIIB-IV melanoma is ongoing. Preliminary data of 18 patients with Stage IIIB–IV M1c melanoma suggest much higher complete and ORRs with the combination than have been seen with either agent alone. (8) ORR was 56% (95% CI 31–79%), with complete responses in 33%, partial responses in 22% and stable disease in 17%. In responders, mean/median time to investigator-assessed response was 18.8/22.9 weeks (range 11.1–25.0). Flow cytometry showed a higher increase in the number of activated CD8 T-cells in patients with disease control. No dose-limiting toxicities were observed, and most reported toxicities were apparently related to ipilimumab. The randomized Phase II portion of the trial is currently ongoing, and a trial in combination with pembrolizumab (MK-3475) in PD-1 blockade naïve melanoma patients is also ongoing.

In this protocol we want to focus on those patients who do not respond to PD-1/L1 blockade because there are no pre-existing tumor antigen-specific T-cells in their tumors ready to attack the cancer, or they are lost after a period of responses. (9,10,11,12,13) We hypothesize that this lack of sufficient immune activation can be addressed by a combination therapy with an immune activating oncolytic virus.

2.2 Local and visceral ORR with talimogene laherparepvec (T-VEC) alone

The OPTiM trial included 3274 evaluable baseline and new lesions from 285 evaluable patients and 259 (91 %) of the 285 evaluable patients had three or more lesions (14).

a. Injected Lesions
Of a total of 2116 lesions injected with T-VEC from 277 patients, 1361 (64 %) lesions had a decrease in size of ≥50 % including 995 (47 %) lesions that resolved completely. Median time to response of responding injected lesions from baseline was 9.3 weeks. Among 277 patients evaluable for response in injected lesions, 37 % had ≥50 % decrease in total tumor area of injected lesions and 16 % had complete resolution of injected lesions. The ORR in these patients was 32 % (15 % CR).

b. Un-injected Non-Visceral Lesions
A total of 981 un-injected, non-visceral lesions (cutaneous, subcutaneous, or nodal) from 177 patients were evaluable, 331 (34 %) lesions decreased in size by ≥50 %, and 212 (22 %) had CR. Among 177 patients evaluable for response, 21 % had ≥50 % decrease in total tumor area of un-injected non-visceral lesions and 14 % CR, which corresponded to an ORR of 18 % and a CR rate of 6 %.

c. Visceral Lesions
Of a total of 177 individual visceral lesions from 79 patients, twenty-seven (15 %) decreased in size by ≥50 %, and 16 (9 %) CR. Evaluable visceral lesions were located in the lung (77 %), liver (8 %), adrenal gland (6 %), spleen (3 %), kidney (3 %), pancreas (1 %), and the thyroid, brain, and gastrointestinal tract (<1 % each). Among responding visceral lesions, 81 % were in the lung, 15 % in the liver, and 4 % in the thyroid. Among 79 patients evaluable for response in visceral lesions, 10 % had a ≥50 % decrease in total tumor area of visceral lesions and 6 % had complete resolution of visceral lesions. ORR was 14 % and the CR rate was 3 %.

2.3 Correlative Studies Background

Please refer to translational medicine proposal.

2.4 Inclusion of Women and Minorities

This study was designed to include women and minorities, but was not designed to measure differences of intervention effects. The anticipated accrual in the ethnicity/race and sex categories is shown in the table below.

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	1	0	0	1
Asian	0	1	0	0	1
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	1	1	0	0	2
White	13	28	1	1	43
More Than One Race	0	0	0	0	0
Total	14	31	1	1	47

3.0 DRUG INFORMATION

Investigator Brochures

For information regarding Investigator Brochures, please refer to SWOG Policy 15.

For this study, talimogene laherparepvec (T-VEC) and pembrolizumab (MK-3475) are investigational and are being provided under an IND held by the National Cancer Institute. The Investigator Brochures may be obtained by accessing PMB's Online Agent Order Processing (OAOP) application (https://ctepcore.nci.nih.gov/OAOP).

Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. Questions about IB access may be directed via email to IBcoordinator@mail.nih.gov or by phone 240/276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET).

3.1 Pembrolizumab (MK-3475) (NSC-776864)

a. Pharmacology

Pembrolizumab (MK-3475) is a humanized MAb of the lgG4/kappa isotype. The programmed cell death 1 (PD-1) receptor is an inhibitory receptor expressed by T-cells. When bound to either of its ligands, PD-L1 or PD-L2, activated PD-1 negatively regulates T-cell activation and effector function. The pathway may be engaged by tumor cells expressing PD-1 ligands to suppress immune control. pembrolizumab (MK-3475) blocks the negative immune regulatory signaling by binding to the PD-1 receptor, inhibiting the interaction between PD-1 and its ligands, and thereby promoting the host immune system to recognize tumor cells as foreign bodies to be eliminated.

b. Pharmacokinetics

The pharmacokinetic profile of pembrolizumab (MK-3475), with low clearance and limited volume of distribution, is typical for therapeutic antibodies. Elimination half-life after IV administration was approximately 14 to 21.6 days. Steady state concentration levels were achieved within 16 weeks of treatment when tested at 3 and 10 mg/kg dosing as administered at 2 week intervals. During repeated dosing of 2 or 10mg/kg Q3W, steady state in trough concentrations appeared to have been achieved after approximately three months. Furthermore, pembrolizumab (MK-3475) has a low potential of eliciting the formation of anti-drug antibodies.

c. Adverse effects

Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 3793 patients.* Below is the CAEPR for pembrolizumab (MK-3475).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.6, July 15, 2021[1]

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 5.0 Term) [n= 3793]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia[2]		

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 5.0 Term) [n= 3793]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Blood and lymphatic system disorders - Other (immune thrombocytopenic purpura)[2]	
	Lymph node pain[2]		
CARDIAC DISORDERS			
		Myocarditis[2]	
		Pericarditis[2]	
ENDOCRINE DISORDERS			
	Adrenal insufficiency[2]		
	Endocrine disorders - Other (thyroiditis)[2]		
	Hyperthyroidism[2]		
	Hypophysitis[2]		
	Hypopituitarism[2]		
	Hypothyroidism[2]		
EYE DISORDERS			
		Uveitis[2]	
		Eye disorders - Other (Vogt-Koyanagi-Harada syndrome)	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Colitis[2]		
	Diarrhea[2]		***Diarrhea[2] (Gr 2)***
	Mucositis oral[2]		
	Nausea		***Nausea (Gr 2)***
	Pancreatitis[2]		
	Small intestinal mucositis[2]		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills[2]		

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 5.0 Term) [n= 3793]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
Fatigue			***Fatigue (Gr 2)***
	Fever[2]		
HEPATOBILIARY DISORDERS			
	Hepatobiliary disorders - Other (autoimmune hepatitis)[2]		
		Hepatobiliary disorders - Other (sclerosing cholangitis)	
IMMUNE SYSTEM DISORDERS			
		Anaphylaxis[2]	
		Cytokine release syndrome[2]	
		Immune system disorders - Other (acute graft-versus-host-disease)[2,3]	
		Immune system disorders - Other (hemophagocytic lymphohistiocytosis)[2]	
	Immune system disorders - Other (pseudoprogression/tumor inflammation)[2]		
	Immune system disorders - Other (sarcoidosis)[2]		
		Serum sickness[2]	
INFECTIONS AND INFESTATIONS			
	Infection[4]		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 5.0 Term) [n= 3793]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Infusion related reaction	
INVESTIGATIONS			
	Alanine aminotransferase increased[2]		
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased[2]		
	Blood bilirubin increased		
	CPK increased		
		GGT increased	
		Serum amylase increased	
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
	Hyponatremia		
		Metabolism and nutrition disorders - Other (diabetic ketoacidosis)[2]	
		Metabolism and nutrition disorders - Other (type 1 diabetes mellitus)[2]	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia[2]		***Arthralgia[2] (Gr 2)***
	Arthritis[2]		
	Avascular necrosis[2]		
	Back pain		
	Joint effusion[2]		
	Joint range of motion decreased		
	Musculoskeletal and connective		

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 5.0 Term) [n= 3793]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	tissue disorder - Other (tenosynovitis)[2]		
	Myalgia[2]		
	Myositis[2]		
NERVOUS SYSTEM DISORDERS			
		Guillain-Barre syndrome[2]	
		Nervous system disorders - Other (myasthenic syndrome)[2]	
		Nervous system disorders - Other (neuromyopathy)[2]	
		Nervous system disorders - Other (non-infectious encephalitis)[2]	
		Nervous system disorders - Other (non-infectious meningitis)[2]	
		Nervous system disorders - Other (non-infectious myelitis)	
		Nervous system disorders - Other (polyneuropathy)[2]	
		Paresthesia	
		Peripheral motor neuropathy[2]	
RENAL AND URINARY DISORDERS			
		Renal and urinary disorders - Other (autoimmune nephritis)[2]	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		
	Pleuritic pain[2]		

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 5.0 Term) [n= 3793]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Pneumonitis[2]		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Bullous dermatitis[2]		
		Erythema multiforme[2]	
	Erythroderma		
		Palmar-plantar erythrodysesthesia syndrome	
	Pruritus[2]		***Pruritus[2] (Gr 2)***
	Rash acneiform[2]		
	Rash maculo-papular[2]		***Rash maculo-papular[2] (Gr 2)***
	Skin and subcutaneous tissue disorders - Other (dermatitis)[2]		
	Skin hypopigmen-tation[2]		
		Stevens-Johnson syndrome[2]	
		Toxic epidermal necrolysis	
	Urticaria[2]		
VASCULAR DISORDERS			
		Vasculitis[2]	

[1] This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2] Immune-mediated adverse reactions have been reported in patients receiving MK-3475 (pembrolizumab). Adverse events potentially related to MK-3475 (pembrolizumab) may be manifestations of immune-mediated adverse events. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of MK-3475 (pembrolizumab), administration of corticosteroids and supportive care.

[3] Acute graft-versus-host disease has been observed in patients treated with MK-

3475 (pembrolizumab) who received hematopoeitic stem cell transplants.

[4] Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on MK-3475 (pembrolizumab) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that MK-3475 (pembrolizumab) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Disseminated intravascular coagulation; Hemolysis

CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Chest pain - cardiac; Heart failure; Myocardial infarction; Pericardial effusion; Pericardial tamponade; Ventricular arrhythmia

EYE DISORDERS - Eye pain

GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Constipation; Duodenal hemorrhage; Dysphagia; Gastritis; Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other (intestinal obstruction); Gastrointestinal disorders - Other (intussusception); Oral pain; Rectal hemorrhage; Small intestinal perforation; Upper gastrointestinal hemorrhage; Vomiting

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema face; Edema limbs; Facial pain; Gait disturbance; General disorders and administration site conditions - Other (general physical health deterioration); Generalized edema; Malaise; Non-cardiac chest pain; Pain

INVESTIGATIONS - Cholesterol high; Creatinine increased; Fibrinogen decreased; Lymphocyte count decreased; Neutrophil count decreased; Platelet count decreased; Weight loss; White blood cell decreased

METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypertriglyceridemia; Hyperuricemia; Hypoalbuminemia; Hypokalemia; Hypophosphatemia; Metabolism and nutrition disorders - Other (failure to thrive); Tumor lysis syndrome

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (groin pain); Pain in extremity

NERVOUS SYSTEM DISORDERS - Aphonia; Depressed level of consciousness; Dysarthria; Edema cerebral; Encephalopathy; Headache; Hydrocephalus; Lethargy; Meningismus; Nervous system disorders - Other (brainstem herniation); Seizure; Syncope; Tremor

PSYCHIATRIC DISORDERS - Agitation; Confusion

RENAL AND URINARY DISORDERS - Acute kidney injury; Nephrotic syndrome; Proteinuria; Renal and urinary disorders - Other (hydronephrosis); Urinary incontinence; Urinary tract pain

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Pelvic pain

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Dyspnea; Hypoxia; Laryngeal inflammation; Pleural effusion; Pneumothorax; Respiratory failure

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Skin and subcutaneous tissue disorders - Other (drug eruption)

VASCULAR DISORDERS - Hypertension; Peripheral ischemia; Thromboembolic event

Note: MK-3475 (pembrolizumab) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

1. Pregnancy and Lactation:

   The central function of the PD-1/PD-L1 pathway is to maintain immune tolerance to the fetal allograft, and its important role in maintaining pregnancy has been recently emphasized in literature [4-6, 4-7] The PD-L1 molecule expressed at the uteroplacental interface effectively protects the concepti from maternal T-cell-mediated immunity. Blockade of PD-L1 signaling has been shown in murine models of allogeneic pregnancy [4-6, 4-7] to abrogate fetomaternal tolerance to the concepti and to result in an increase in fetal resorption. The evidence from these experimental results indicates that there is a theoretical risk associated with the administration of pembrolizumab (MK-3475) to women of child-bearing potential (WOCBP). It is therefore anticipated that the inhibition of PD-1 by treatment with anti-PD-1 monoclonal antibody (i.e., pembrolizumab) during pregnancy would have detrimental effects that might include increased rates of abortion and stillbirth. Women/men of reproductive potential should use an effective contraceptive method while on treatment and through 120 days after the last dose of pembrolizumab (MK-3475).

   It is not known whether pembrolizumab (MK-3475) is excreted in human milk. Because of the potential for drugs to be excreted in human milk, the risk to the nursing infant cannot be excluded and therefore pembrolizumab (MK-3475) should not be administered to nursing mothers.

2. Drug Interactions:
   No studies on pharmacodynamic drug interactions have been performed. Due to potential drug interactions, a complete patient medication list, including pembrolizumab (MK-3475), should be screened prior to initiation of and during treatment with pembrolizumab (MK-3475). See Section 8.0 Toxicities to be Monitored and Dosage Modifications

d. Dosing and Administration

   See Section 7.0 Treatment Plan

e. How Supplied

   Pembrolizumab (MK-3475) is supplied by Merck & Co., Inc. and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI. Pembrolizumab (MK-3475) injection is a sterile, preservative-free, clear to opalescent, colorless to slightly yellow solution for intravenous use. Each vial contains 100 mg of pembrolizumab (MK-3475) in 4 mL of solution. Each 1 mL of solution contains 25 mg of pembrolizumab (MK-3475) and is formulated in: L-histidine (1.55 mg), polysorbate 80 (0.2mg), sucrose (70 mg), and Water for injection, USP.

f. Storage, Preparation & Stability

1. Preparation:

Pembrolizumab (MK-3475) solution for infusion must be diluted prior to administration. Allow the required number of vials to equilibrate to room temperature. Do not shake the vials. Do not use if opaque or extraneous particulate matter other than translucent to white proteinaceous particles is observed. Do not use if discolored. To prepare the infusion solution add the dose volume of pembrolizumab (MK-3475) to an infusion bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Gently invert the bag 10-15 times to mix the solution. The final concentration must be between **1 mg/mL to 10 mg/mL.**

Compatible IV bag materials: PVC plasticized with DEHP, non-PVC (polyolefin), EVA, or PE lined polyolefin

2. Storage:

Store intact vials between 2°C - 8°C (36°F - 46°F). Do not freeze. Protect from light by storing in the original box.

If a storage temperature excursion is identified, promptly return pembrolizumab (MK-3475) to between 2-8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

3. Stability:

Refer to the package insert for expiration.

Administer prepared solutions immediately after preparation. If not administered immediately, prepared solutions may be stored refrigerated for up to 24 hours. Pembrolizumab (MK-3475) solutions may be stored at room temperature for a cumulative time of up to 6 hours. This includes room temperature storage of liquid drug product solution in vials, room temperature storage of infusion solution in the IV bag, and the duration of infusion.

4. Route of Administration:

IV infusion only. Do not administer as an IV push or bolus injection.

5. Method of Administration:

Infuse over approximately 30 minutes (range: 25 - 40 minutes) using an infusion set containing a low-protein binding 0.2 to 5 µm in-line filter made of polyethersulfone or polysulfone. Infusion rate should not exceed 6.7 mL/min. A central line is not required; however if a subject has a central venous catheter in place, it is recommended that it be used for the infusion. Do not co-administer other drugs through the same infusion line. Following the infusion, flush the IV line with normal saline.

Compatible infusion set materials: PVC plasticized with DEHP or DEHT, PVC and tri-(2-ethylhexyl) trimellitate, polyethylene lined PVC, polyurethane, or polybutadiene.

g. Drug Ordering & Accountability

1. Drug Ordering

Starter supplies will not be provided. NCI supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that drug be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP assigned protocol number (**S1607**) must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 and a CV. If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution. Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the -establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

Confirmation of patient's enrollment is required for initial supply.

2. Drug Handling and Accountability (NCI logs or other)
The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

3. Drug return and/or disposition instruction

Drug Expiration: PMB will send a stock recovery letter when the agent is no longer suitable for use. All undispensed drug supplies should be returned to the PMB. When it is necessary to return study drug, investigators should return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov).

h. Contact Information

CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/

NCI CTEP Investigator Registration: PMBRegPend@ctep.nci.nih.gov

PMB policies and guidelines:
http://ctep.cancer.gov/branches/pmb/agent_management.htm

PMB Online Agent Order Processing (OAOP) application:
https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx

CTEP Identity and Access Management (IAM) account: https://eapps-ctep.nci.nih.gov/iam/

CTEP Associate Registration and IAM account help: ctepreghelp@ctep.nci.nih.gov

PMB email: PMBAfterHours@mail.nih.gov

PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

3.2 Talimogene Laherparepvec (T-VEC, AMG 678; OncoVEX^{GM-CSF}, IMLYGIC ™) (NSC 785349)

a. Pharmacology

1. Classification: Oncolytic immunotherapy.

2. Product Description:

Talimogene laherparepvec (T-VEC) is an investigational oncolytic virus based on a modified herpes simplex virus type-1 (HSV-1). It selectively replicates in tumor tissue and induces oncolysis of tumor cells resulting in a systemic antitumor immune response specific to subjects' tumor.

3. Mechanism of Action:

Talimogene laherparepvec (T-VEC) is an attenuated herpes simplex virus type 1 (HSV-1) derived by functional deletion of 2 genes, ICP34.5 and ICP47, and insertion of coding sequence for human granulocyte macrophage colony stimulating factor (GM-CSF). Deletion of ICP34.5 allows T-VEC replication in tumor tissue; normal cells are able to protect against T-VEC infection as they contain intact anti-viral defense mechanisms. Deletion of ICP47 prevents down-regulation of antigen presentation molecules and increases the expression of HSV US11 gene, which enhances viral replication in tumor cells. GM-CSF recruits and activates antigen presenting cells which can process and present tumor-derived antigens to promote an effector T-cell response.

Talimogene laherparepvec (T-VEC) was approved for intratumoral injections in cutaneous, subcutaneous and/or nodal lesions at the following dose and schedules:

- 1st dose at 1 x 10^6 PFU/mL for a maximum volume of 4mL
- •2nd dose 3 weeks later at 1 x 10^8PFU/mL for a maximum of 4mL

All sequence doses every two weeks at 10^8PFU/mL for a maximum of 4mL for treatment with single agent Talimogene laherparepvec (T-VEC). In this protocol Talimogene laherparepvec (T-VEC) is given every three weeks.

b. Pharmacokinetics and activity of talimogene laherparepvec (T-VEC)

1. Absorption:
Talimogene laherparepvec (T-VEC) is injected directly into the tumor lesions.

2. Pharmacokinetics of Talimogene laherparepvec (T-VEC):

The biodistribution and shedding of intralesionally administered talimogene laherparepvec (T-VEC) are being investigated in an ongoing study measuring talimogene laherparepvec (T-VEC) DNA and virus in blood, oral mucosa, urine, injection site, and occlusive dressings. In the initial 20 patients with melanoma who received talimogene laherparepvec (T-VEC) intralesional injection at a dose and schedule similar to that of the clinical study, available data indicate that talimogene laherparepvec (T-VEC) DNA was present in the blood in 17 (85%) patients and in urine of 4 (20%) patients during the study. The peak levels of talimogene laherparepvec (T-VEC) DNA in the urine were detected on the day of treatment. Infectious talimogene laherparepvec (T-VEC) virus was detected at the site of injection in 3 (15%) patients at a single time point each, and all within the first week after the initial injection. The exterior of the occlusive dressings was positive for talimogene laherparepvec (T-VEC) DNA in 14 (70%) patients during the study; however, no infectious virus was detected on the exterior of the occlusive dressing. The number of patients with measurable levels of talimogene laherparepvec (T-VEC) DNA on the exterior of occlusive dressings declined over time with no measurable DNA by the third treatment in 13 patients tested.

3. Antitumor Activity:

Talimogene laherparepvec (T-VEC) demonstrated initial biological activity as monotherapy in subjects with advanced solid tumors with metastases in the skin or subcutaneous (SC) tissue as evidenced by necrosis or apoptosis in tumor biopsies (Study 001/01).

In a phase III trial in melanoma (Study 005/05 “A Randomized Phase III Clinical Trial to Evaluate the Efficacy and Safety of treatment with OncoVEXGM-CSF Compared to Subcutaneously Administered GM-CSF in Melanoma Patients with Unresectable Stage IIIb, IIIc and IV Disease”), talimogene laherparepvec (T-VEC) demonstrated an improvement in the primary endpoint, durable response rate (DRR) (defined as complete response [CR] or partial response [PR] maintained for ≥ 6 months continuously and which had its onset on the first 12 months of treatment): 16.3% vs. 2.1%. Overall survival (OS) was a secondary endpoint. At the primary analysis, median OS was 23.3 (95% confidence interval [CI]: 19.5, 29.6) months in the talimogene laherparepvec (T-VEC) arm and 18.9 (95% CI: 16.0, 23.7) months in the GM-CSF arm (hazard ratio [HR] 0.79; 95% CI: 0.62, 1.00; p = 0.051). At final analysis, with an additional follow-up of 5 months (median 49 months [range, 37-63]), median OS remained 4.4 months longer for talimogene laherparepvec (T-VEC) compared with GM-CSF (23.3 vs 18.9 months; HR 0.79, 95% CI: 0.62-1.00, P = 0.0494, descriptive). Results from the phase 2 study in melanoma (002/03) also support the efficacy of talimogene laherparepvec (T-VEC) for the treatment of melanoma.

Response to talimogene laherparepvec (T-VEC) can be delayed, and the phenomenon sometimes referred to as "pseudoprogression" has been observed. In the pivotal clinical trial, the median time to response onset was 4.1 months (ranged from 1.2 to 16.7 months). Approximately 50% of the patients ultimately achieved a response had evidence of increase in the size of existing lesions and/or development of new lesions. Pseudoprogression can also be seen with other immunotherapies. Patients may continue treatment if there was increase in the size of existing lesions or development of new lesions, as long as the investigator determined that initiation of a new treatment was not required.

c. Talimogene laherparepvec (T-VEC) Safety Profile:

As of a June 30, 2015 data cutoff, 486 subjects have received talimogene laherparepvec (T-VEC) (with doses from 104 to 108 PFU/mL) and have provided safety data across 15 studies (Investigator's Brochure, 2015). Thirty-one of these subjects continued into the extension phase of two of these studies; a detailed summary of safety results is available in Table 6-3 of the Talimogene Laherparepvec Investigator's Brochure (2015).

Overall, most adverse events (AEs) reported in subjects administered talimogene laherparepvec (T-VEC) are non-serious and primarily include flu-like symptoms and injection site reactions (Investigator's Brochure, 2015). Most fatal AEs reported in subjects administered talimogene laherparepvec (T-VEC) were reported in the setting of disease progression. In the Phase III study (005/05), the three most frequent AEs observed in the talimogene laherparepvec (T-VEC) group were fatigue (36.2% GM-CSF, 50.3% talimogene laherparepvec (T-VEC), chills (8.7%, 48.6%, respectively), and pyrexia (8.7%, 42.8%, respectively). The following table also include AEs that occurred with a higher incidence in the talimogene laherparepvec (T-VEC) group compared with the GM-CSF group.

d. Important Identified Risks with Talimogene laherparepvec (T-VEC):

1. Injection site reactions:

Talimogene laherparepvec (T-VEC) has been injected into cutaneous, subcutaneous and nodal tumor lesions. Injection site reactions may include erythema, discoloration, induration and pain. Necrosis at injected site may also occur.

2. Cellulitis at site of injection:

Intra-lesional administration of talimogene laherparepvec (T-VEC) has been associated with cellulitis at the injection site, and systematic infection may develop. In the Phase III melanoma clinical study, the incidence of AEs in the bacterial cellulitis category was 6.2% in the T-VEC group (vs. 1.6% in the GM-CSF group).

3. Impaired wound healing at site of injection:

Impact healing at the injection site has been reported, and the risk may be increased in settings with underlying risk factors (e.g. previously radiated or poorly vascularized areas). One patient with peripheral vascular disease had an amputation of lower extremity due to injection of non-healing wound after talimogene laherparepvec (T-VEC) injection. In the Phase III melanoma clinical study, the impaired wound healing occurred

in 5.5% of patients in the talimogene laherparepvec (T-VEC) group (vs. 2.4% in the GM-CSF group).

4. Immune-mediated AEs:

   Across melanoma studies, immune-mediated adverse events considered possibly related to talimogene laherparepvec (T-VEC) were reported in 2% of subjects treated with talimogene laherparepvec (T-VEC) (and included events of vasculitis, glomerulonephritis, acute renal failure, pneumonitis, and worsening psoriasis. Most cases were grade 2 or 3. One grade 4 case (glomerulonephritis) was reported, which resolved with treatment, and no fatal cases were reported. Other contributory factors were identified in several of these cases, including pre-existing immune-mediated conditions, other concurrent medications, and intercurrent medical events.

5. Plasmacytoma at the injection site:

   A case was reported in the Phase III melanoma clinical study. The plasmacytoma developed the area of the injected tumor on the scalp after 9 cycles of treatment with talimogene laherparepvec (T-VEC). On medical review, the event was felt to be consistent with recruitment of plasma cells in response to the talimogene laherparepvec (T-VEC) injections and the patient had a pre-existing (smoldering) multiple myeloma. This case was considered possibly related to the treatment. No other cases of plasmacytoma have been reported in clinical trials with talimogene laherparepvec (T-VEC) to date.

6. Obstructive airway disorder:

   In the Phase III melanoma clinical study (005/05), one (0.3%) subject treated with talimogene laherparepvec (T-VEC) reported the adverse event of obstructive airways disorder. The event was grade 4 and resolved with sequelae. The female subject was previously treated with high-dose interleukin-2 and experienced an acute respiratory failure requiring intubation. The subject complained of breathing problems after discharge. Four to 6 weeks later, she received the first dose of talimogene laherparepvec (T-VEC) (two 1 - 1.5 cm lesions in the right supraclavicular fossa). Thirteen days after the second talimogene laherparepvec (T-VEC) dose, the subject presented with acute respiratory distress requiring an emergency tracheostomy. Imaging showed a mass in the larynx on the contralateral side and adjacent lymph node. Etiology of the laryngeal mass was unclear. A temporal relationship to talimogene laherparepvec (T-VEC) treatment was present. Study medication was permanently discontinued.

7. Disseminated herpetic infection in SEVERELY immunocompromised individuals (defined as those with any severe congenital or acquired cellular and/or humoral immune deficiency):

   Talimogene laherparepvec (T-VEC) has not been studied in immunocompromised patients. However, based on animal data (see Section 5.2 of IB), patients who are severely immunocompromised (e.g., patients with severe congenital or acquired cellular and/or humoral immune deficiency) may be at an increased risk of disseminated herpetic infection and should not be treated with talimogene laherparepvec (T-

VEC). "Disseminated herpetic infection in severely immunocompromised individuals" is defined as an important identified risk based on preclinical toxicology with talimogene laherparepvec (T-VEC) as well as clinical observations of wild-type HSV-1 infection in immunocompromised patients. In preclinical studies in 100% SCID mice (devoid of T and B cells) and 20% BALB/c nude mice (deficient in T cells and partially deficient in B cell function), viral inclusion bodies and necrosis were observed in multiple organs, including neurons of the GI tract, adrenal gland, eyes, skins and brain.

8. Deep vein thrombosis.

e. Important Potential Risks with Talimogene laherparepvec (T-VEC):

1. Disseminated herpetic infection in immunocompromised individuals (defined as those with HIV/ AIDS, leukemia, lymphoma, common variable immunodeficiency, or those who require high-dose steroids or other immunosuppressive agents):

   Note, for patients who are severely immunocompromised (completely lacking T with complete or partially impaired B cell function), disseminated herpetic infection is an "identified" AE (see section of talimogene laherparepvec (T-VEC) Identified Risks. It is unknown whether patients who are not severely immunocompromised (those with conditions limited to T cell dysfunction such as HIV, AIDS, or patients with common variable immunodeficiency or those who require chronic treatment with steroids or other immunosuppressive agents) are at increased risk. The potential risk of disseminated herpetic infection and the potential benefits of treatment should be considered before administering talimogene laherparepvec (T-VEC) to these patients.

2. Symptomatic talimogene laherparepvec (T-VEC) infection in normal tissues:

   In mouse tumor models, viral lysis/tissue injury was limited to tumors in immunocompetent animals. There was no clinical or pathological evidence of symptomatic infection or injury to normal tissues after repeated intratumoral, intravenous, or subcutaneous injection, including mice dosed with up to 10^7 PFU talimogene laherparepvec (T-VEC) (~60-fold over the highest proposed clinical dose, on a PFU/kg basis) via weekly subcutaneous injection for up to 3 months.

   No human cases of confirmed infection of non-tumor tissues by talimogene laherparepvec (T-VEC) have been reported. While 5.5% of patients treated with talimogene laherparepvec (T-VEC) (vs 1.6% in the BM-CSF group) reported oral or corneal herpes infection, it is not confirmed whether the source was wide-type herpes or talimogene laherparepvec (T-VEC). Patients who develop herpes-like lesions should follow stand hygienic practice to prevent viral transmission.

3. Symptomatic herpetic infection due to latency and reactivation of talimogene laherparepvec (T-VEC) or wild-type HSV-1:

Co-infection of neurons already harboring latent wild-type HSV-1 by talimogene laherparepvec (T-VEC) could potentially stimulate the reactivation of latent wild-type HSV-1 in patients with prior infection.

Talimogene laherparepvec (T-VEC) Infection of tumor or non-tumor tissues could potentially lead to establishment of latency and subsequent reactions of talimogene laherparepvec (T-VEC) if the virus comes into contact with axonal nerve terminals and was transported to neuronal cell bodies. In mice, biodistribution studies have detected low levels of talimogene laherparepvec (T-VEC) in trigeminal ganglia through 28 days in 1 of 6 animals following high-dose IV administration (0.6×10^6 PFU, ~36-fold over the highest proposed clinical dose). Talimogene laherparepvec (T-VEC) was undetectable in trigeminal ganglia in mice after subcutaneous administration.

4. Recombination of talimogene laherparepvec (T-VEC) with wild-type HSV-1:

This event has not been reported in the Phase III melanoma clinical study. The genetic modifications made to talimogene laherparepvec (T-VEC) only attenuate the virus, either by limiting replication to tumor cells and neurovirulence (by deletion of ICP34.5) or enhancing immune detection of infected cells (by eliminating ICP47), none of the theoretical products of recombination between wild-type HSV-1 and talimogene laherparepvec (T-VEC) would have increased virulence. The likelihood of recombination occurring is low, and if recombination occurred, the virulence of the recombinants would be no greater than wild-type HSV-1, and symptoms will be reduced compared to wild-type HSV-1. Management with systemic antivirals would be the same.

5. Talimogene laherparepvec (T-VEC)-mediated anti-GM-CSF antibody response:

There is a theoretical concern that transgene-derived expression of GM-CSF could induce an immune response reactive with endogenous GM-CSF. Autoantibodies against GM-CSF is detected in 9.6% general population. It is not known whether such phenomena could be expected with the limited exposure anticipated with transgene expression of GM-CSF from talimogene laherparepvec (T-VEC).

f. Special Precautions:

1. Accidental exposure of healthcare providers (HCP) to talimogene laherparepvec (T-VEC):

A needle stick injury, spill, or splash back during administration may result in accidental exposure of healthcare providers (HCPs) to talimogene laherparepvec (T-VEC). The ICP34.5 gene deletion is intended to allow only tumor selective replication and limited or no viral replication in normal tissues. The signs or symptoms of primary infection at the site of exposure are expected to be similar to what is seen with wild-type HSV-1. The severity of symptoms is expected to be reduced compared to what is seen with wild-type HSV-1. Talimogene laherparepvec (T-VEC) is sensitive to acyclovir. In one case of exposure of study personnel to talimogene

laherparepvec (T-VEC), the exposed physician developed clinical signs of a herpetic whitlow-like lesion at the site of an accidental needle stick that resolved after treatment with acyclovir.

2. Transmission of talimogene laherparepvec (T-VEC) from patient to close contacts or HCPs via direct contact with infected lesions or body fluids resulting in symptomatic infection (primary or reactivation):

   A clinical study is in progress to inform whether talimogene laherparepvec (T-VEC) is present in saliva or oral or genital secretions of treated patients. The likelihood of transfer of talimogene laherparepvec (T-VEC) to a close contact or HCP increases if the contact has a break in the skin or mucous membranes. Signs or symptoms of infection would be anticipated to be similar to signs and symptoms of wild-type HSV infection, although the reduced potential to replicate in normal tissue may result in less severe clinical manifestations. Shedding results showed that talimogene laherparepvec (T-VEC) was detected on the surface of injected lesions for up to 2 weeks after injection in 8 of 72 (11%) subjects. Virus was not detected on the exterior surface of tumor dressings at any time point tested.

3. Loss of efficacy in patients treated with systemic acyclovir for complications:

   Talimogene laherparepvec (T-VEC) retained an intact thymidine kinase gene, and is therefore sensitive to acyclovir and acyclovir may attenuate activity of talimogene laherparepvec (T-VEC). The risks and benefits of talimogene laherparepvec (T-VEC) treatment before administering acyclovir or other anti-viral agents indicated for management of herpetic infection will need to be considered. Other treatments, such as foscarnet, may be used as an alternative for acyclovir.

g. Effects

1. Comprehensive Adverse Effects and Potential Risk List(s) CAEPRs):

   The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 389 patients.* Below is the CAEPR for talimogene laherparepvec (T-VEC).

   NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.1, August 22, 2017[1]

Adverse Events with Possible Relationship to Talimogene laherparepvec (T-VEC, IMLYGIC) (CTCAE 5.0 Term) [n= 517]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Constipation		***Constipation (Gr 2)***
	Diarrhea		***Diarrhea (Gr 2)***
Nausea			***Nausea (Gr 2)***
Vomiting			***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Chills			***Chills (Gr 2)***
Fatigue			***Fatigue (Gr 2)***
Fever			***Fever (Gr 2)***
Flu like symptoms			***Flu like symptoms (Gr 2)***
Injection site reaction[2]			***Injection site reaction[2] (Gr 2)***
	Pain[3]		***Pain[3] (Gr 2)***
IMMUNE SYSTEM DISORDERS			
		Autoimmune disorder[4]	
INFECTIONS AND INFESTATIONS			
	Infections and infestations - Other (herpetic keratitis)		
	Infections and infestations - Other (oral herpes)		
	Skin infection[5]		***Skin infection[5] (Gr 2)***
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Wound complication[6]		
INVESTIGATIONS			
	Weight loss		***Weight loss (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
	Dehydration		

Adverse Events with Possible Relationship to Talimogene laherparepvec (T-VEC, IMLYGIC) (CTCAE 5.0 Term) [n= 517]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 2)***
	Myalgia		***Myalgia (Gr 2)***
	Pain in extremity		***Pain in extremity (Gr 2)***
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
		Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (plasmacytoma at the injection sites)	
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Headache		***Headache (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pharyngolaryn-geal pain		***Pharyngolaryn-geal pain (Gr 2)***
		Respiratory, thoracic and mediastinal disorders - Other (obstructive airway disorder)[7]	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Pruritus		
	Rash[8]		
	Skin and subcutaneous tissue disorders - Other (dermatitis)		
	Skin and subcutaneous tissue disorders - Other (vitiligo)[4]		
VASCULAR DISORDERS			
	Flushing		
	Thromboembolic event (venous)		

Adverse Events with Possible Relationship to Talimogene laherparepvec (T-VEC, IMLYGIC) (CTCAE 5.0 Term) [n= 517]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Vascular disorders - Other (carotid artery blowout syndrome)[9]	

[1] This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting pio@ctep.nci.nih.gov. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.
[2] Injection site reactions may include redness, swelling, and bleeding.
[3] Pain can occur in the tumor, injection sites and nodal draining (axilla and groin etc) lymph nodes.
[4] Several events which are autoimmune-mediated, such as acute kidney injury (acute renal failure), glomerulonephritis (nephritis), worsening of psoriasis, pneumonitis, vasculitis, and vitiligo (areas of skin with loss of color) have been observed in clinical trials of talimogene laherparepvec.
[5] Skin infection (cellulitis) can be complicated with local and systemic infection, tissue necrosis, and ulceration, or wound complications.
[6] Wound complication may occur at the injection site and may include wound infection and poor healing.
[7] Obstructive airway disorder has occurred in one patient with Head and Neck Squamous cell carcinoma (HNSCC) with a suproventricular mass who developed acute respiratory distress requiring a trachetomy 13 days after the second dose of T-VEC. Imaging showed a mass in the larynx and adjacent lymph nodes on the contralateral side.
[8] Rash may include rash maculo-papular and erythematous rash.
[9] Carotid artery blowout syndrome was observed in a HNSCC patient treated with T-VEC in combination with anti-PD-1 who had been previously treated with localized (neck) radiation and lymph node dissection.

Adverse events reported on talimogene laherparepvec (T-VEC, IMLYGIC) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that talimogene laherparepvec (T-VEC, IMLYGIC) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia
CARDIAC DISORDERS - Sinus tachycardia
EAR AND LABYRINTH DISORDERS - Tinnitus
GASTROINTESTINAL DISORDERS - Ascites; Dry mouth; Dysphagia; Gastrointestinal disorders - Other (odynophagia); Mucositis oral
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema limbs; Malaise
INFECTIONS AND INFESTATIONS - Infections and infestations - Other (oral candidiasis)

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising; Dermatitis radiation; Fracture
INVESTIGATIONS - Neutrophil count decreased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Hypokalemia
NERVOUS SYSTEM DISORDERS - Cognitive disturbance; Dysgeusia
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Insomnia
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Dyspnea; Pneumonitis[4]

Note: Talimogene laherparepvec (T-VEC, IMLYGIC) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Note: In animal models talimogene laherparepvec has demonstrated several potential risks as detailed below:

1) Talimogene laherparepvec has **not** been tested in severely immune compromised patients. In animal models, injection of talimogene laherparepvec in immune-deficient mice resulted in disseminated infection.
2) Transmission of talimogene laherparepvec to health care professionals and personnel in close contact is possible.
3) Latent infection of talimogene laherparepvec in the neurological system has been observed in mice at high dose of T-VEC, although the clinical implication in human patients is not clear.

2. Pregnancy and Lactation:

Adequate and well-controlled studies with talimogene laherparepvec (T-VEC) in pregnant women have not been conducted. In animal studies, no effects on embryo-fetal development have been seen. In pregnant women who have an infection with wild-type HSV-1 (primary or reactivation), there is potential for the virus to cross the placental barrier and also a risk of transmission during birth due to viral shedding. Infections with wild-type HSV-1 have been associated with serious adverse effects, including multi-organ failure and death, if a fetus or neonate contracts the wild-type herpes infection. While there are no clinical data to date on talimogene laherparepvec (T-VEC) infections in pregnant women, if talimogene laherparepvec (T-VEC) were to act like wild-type HSV-1, there is potential risk to the fetus or neonate. Women of childbearing potential and men should be advised to use an effective method of contraception to prevent pregnancy prior to study entry, during the study participation, and for four months after the last dose of talimogene laherparepvec (T-VEC). Per the IMLYGIC™ package insert, talimogene laherparepvec (T-VEC) is contraindicated during pregnancy.

There is no information regarding the transfer of talimogene laherparepvec (T-VEC) into human milk and its effects on milk production. According to the manufacturer's package insert, it is recommended to either discontinue nursing or to discontinue talimogene laherparepvec (T-VEC) while nursing.

3. Drug Interactions:

No drug interaction studies have been conducted with talimogene laherparepvec (T-VEC), however, talimogene laherparepvec (T-VEC) is sensitive to acyclovir. Acyclovir or other anti-herpetic viral agents may interfere with the effectiveness of talimogene laherparepvec (T-VEC).

h. Dosing & Administration

See Section 7.0 Treatment Plan

1. Dose and Schedule of T-VEC:

a. 1st dose of T-VEC: 1 x 10^6 PFU/mL with a maximum volume of 4 mL with all lesions combined (or according to the dose escalation schedule for Phase I trial).
b. 2nd dose: Should be at least 3 weeks AFTER the 1st dose (To allow for development of neutralization anti-herpes antibodies): 1 x 10^8 PFU/mL with a maximum volume of 4 mL with all lesions combined (or according to the dose escalation schedule for Phase I trial).

2. Special handling and precautions:

a. T-VEC is an attenuated version of HSV-1. Use protective equipment when preparing and administering this agent according to the institutional guidelines. In the event of an accidental occupational exposure through a splash to the eyes or mucous membranes, flush with clean water for at least 15 minutes. In the event of exposure to broken skin or needle stick, clean the site thoroughly with soap and water or a virucidal disinfectant such as 1% sodium hypochlorite or Virkon®.

b. In the event of a secondary exposure (e.g., leakage through occlusive dressing to subject or contacts) to T-VEC, clean the site thoroughly with soap and water or a virucidal disinfectant. Seek healthcare provider for signs of systemic (fever, aches, nausea, and malaise) or local (fever, pain, redness and swelling) infection.

c. Healthcare providers who are immunocompromised or pregnant should not administer talimogene laherparepvec (T-VEC) and should not come into direct contact with talimogene laherparepvec (T-VEC) injection sites or body fluids of treated patients.

d. See Section 3.2f.2 for additional handling precautions.

3. Administration:

a. Route of Administration: Intratumoral/intralesional injection

b. Talimogene laherparepvec (T-VEC) is to be administered by intralesional injection into cutaneous, subcutaneous and nodal lesions with or without image ultrasound guidance. Talimogene laherparepvec (T-VEC) must not be administered into visceral

organ metastases. Do NOT administer talimogene laherparepvec (T-VEC) intravenously.

The volume of talimogene laherparepvec (T-VEC) to be injected into each lesion is depended on the size of the lesion. The total injection volume at each treatment visit should not exceed 4mL for all injected lesions combined.

Injection site may be pre-treated with a topical or a local anesthetic agent; however, a local anesthetic must not be injected directly into the lesion. Clean the lesion and surrounding areas with an alcohol swab and let dry.

c. Talimogene laherparepvec (T-VEC) injection volume guideline:

Lesions should be injected until either the maximum volume is reached or there are no further injectable lesions (as determined by the treating investigator), whichever comes first. The total injection volume for each treatment visit should not exceed 4 mL for all injected lesions combined.

Tumor Size (longest dimension)	Maximum Injection Volume PER Lesion
> 5 cm	4mL
> 2.5 cm to 5cm	2 mL
> 1.5 cm to 2.5 cm	1 mL
> 0.5 cm to 1.5 cm	0.5 mL
≤ 0.5 cm	0.1 mL

4. Intralesional injection guidance:

All reasonably injectable lesions (cutaneous, subcutaneous and nodal disease that can be injected with or without ultrasound guidance) should be injected with the maximum dosing volume available on an individual dosing occasion. On each treatment day, prioritization of injections is recommended as follows:

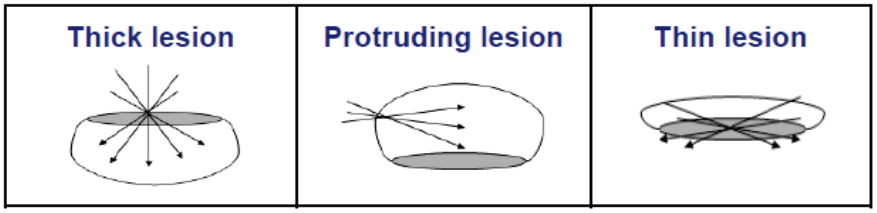
- any new injectable tumor that has appeared since the last injection;
- by tumor size, beginning with the largest tumor;
- any previously uninjectable tumor(s) that is now injectable.

Within the injection volume guidelines in the table above, it is recommended that each lesion receive the maximum amount possible at each visit before moving on to the next lesion, subject to tumor-specific limitations (such as inability to inject the full amount into the lesion). Lesions should be injected until the maximum volume per day (4mL) has been reached or there are no further injectable lesions, whichever comes first.

a. A single point of injection is recommended; multiple insertion points may be used if the tumor is larger than the radial reach of the needle.

b. Inject talimogene laherparepvec (T-VEC) along multiple different tracks within the lesion in order to obtain as wide a dispersion as possible.

c. Distribute talimogene laherparepvec (T-VEC) within the lesion through the insertion point using the radial reach of the needle in different directions to evenly distribute.



d. Avoid premature extraction of the needle.

e. After dosing, the injection site should be swabbed with alcohol and pressure should be applied with gauze for several seconds after injection.

f. Cover the injection site with an absorbent pad and dry occlusive dressing.

g. Injected lesion care: see Section 18.6.

5. Disposal

Dispose of all materials that have come in contact with talimogene laherparepvec (T-VEC) (e.g., vial, syringe, needle, any cotton or gauze) in accordance with local institutional procedure for biohazardous drugs.

i. How Supplied

1. Amgen supplies talimogene laherparepvec (T-VEC) and the Pharmaceutical Management Branch distributes.

There are two nominal vials concentrations:

- 1 x 10^6 PFU/mL packaged as 10 vials per box
- 1 x 10^8 PFU/mL packaged as 20 vials per box

2. Both vial strengths contain 1 mL extractable volume (with approximately 0.1 mL overfill volume) of talimogene laherparepvec solution consisting of disodium hydrogen phosphate dehydrate, sodium dihydrogen phosphate dehydrate, sodium chloride, sorbitol, myo-inositol and Water for Injection. T-VEC is a sterile, semi-translucent to opaque suspension, practically free from particles, preservative free frozen liquid packaged in a single-use 2 mL Crystal Zenith Resin vial. Each vial is sealed with a gray stopper (latex-free) and is Fluorotec-coated on the product side.

3. Current supplies of talimogene laherparepvec are provided as a preservative-free solution in a single-use vial without a clear copolyester plastic sleeve.

   In early 2019, talimogene laherparepvec vials will change in appearance only. Supplies will be transitioned to single-use vials permanently inserted into a clear copolyester plastic sleeve. The product label will be found on the vial sleeve. Talimogene laherparepvec vial is compatible with the Closed System Transfer Device (CSTD), PhaSeal CSTD.

j. Storage, Preparation and Stability

1. Storage:

   Talimogene laherparepvec intact vials are stable between -90°C and -70°C, protect from light. [Note: Frost-free, auto defrosts freezers must not be used since they cycle to warmer temperatures several times a day.]

Freezer Set Point	Acceptable Range
-80°C	-90°C to -70°C

Stability: Shelf-life surveillance of the intact vials is on-going.

If a storage temperature excursion is identified, promptly store talimogene laherparepvec to between -90°C and -70^{0}C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

2. Preparation

   a. Special handling and precautions:

      1. Talimogene laherparepvec (T-VEC) is a live attenuated HSV-1. When preparing, follow local institutional guidelines for handling, personal protective equipment, accidental spills, and waste disposal of biohazard material.

      2. Healthcare providers who are immunocompromised or pregnant should not prepare talimogene laherparepvec (T-VEC).

      3. Wear personal protective equipment including gown, gloves, mask and safety glasses or face shield.

      4. Avoid accidental exposure to talimogene laherparepvec (T-VEC), especially contact with skin, eyes, and mucous membranes.

      5. Cover any exposed wounds before handling.

      6. In the event of an accidental occupational exposure (e.g., through a splash to the eyes or mucous membranes), flush with clean water for at least 15 minutes.

7. In the event of exposure to broken skin or needle stick, clean the affected area thoroughly with soap and water and/or a virucidal disinfectant such as 1% sodium hypochlorite or Virkon®.

8. Seek healthcare provider for signs of systemic (fever, aches, nausea, and malaise) or local (fever, pain, redness and swelling) infection.

9. Treat all talimogene laherparepvec (T-VEC) spills with a virucidal agent such as 1% sodium hypochlorite and blot using absorbent materials.

10. Dispose of all materials that may have come in contact with talimogene laherparepvec (T-VEC) (e.g., vial, syringe, needle, cotton gauze, gloves, masks, or dressings) in accordance with institution biohazard procedure.

11. In the event of a secondary exposure (e.g., leakage through occlusive dressing to subject or contacts) to talimogene laherparepvec (T-VEC), clean the site thoroughly with soap and water or a virucidal disinfectant. Seek healthcare provider for signs of systemic (fever, aches, nausea, and malaise) or local (fever, pain, redness and swelling) infection.

b. Patient Care Implications:

1. Advise patients on the potential for secondary exposure, e.g., broken skin. Advise patients on careful wound care.

2. Necrotic or ulcerating lesions may occur and may be predisposed to local and/or systemic infections such as cellulitis, bacteremia, etc. Advise patients on careful wound care. Infection precautions are recommended for tumor necrosis that results in open wounds.

3. There is a potential risk for exposure of talimogene laherparepvec (T-VEC) from patients to anyone in direct contact with the patient. Individual with open skin lesions and immunosuppressant should not come in contact with talimogene laherparepvec (T-VEC) injection site or its protective dressing.

4. An Information Sheet about talimogene laherparepvec (T-VEC) and the risk of transmission and accidental exposure should be provided to patient's Health Care Providers and Close Contacts (see Sections 18.4 and 18.5)

c. Thawing of talimogene laherparepvec (T-VEC):

1. Remove frozen agent vial from freezer

2. Determine the total volume required for injection.

3. Thaw frozen vials at room temperature, 15ºC to 30ºC (59ºF to 86ºF) until liquid (approximately 30 minutes). Do not expose vial to higher temperatures. Protect vial from light during the thaw process.

4. DO NOT shake vial
5. Gently swirl for completion of thaw.

6. Carefully check the vial for cracks

7. DO NOT re-freeze thawed vial.

d. After Thawing:

1. Gently swirl the vial to ensure the contents are mixed to a homogeneous solution free of ice.

2. Carefully check the vial for damage (e.g., cracks). Dispose of damaged vial(s) according to the institutional policy and guidelines and notify PMB at pmbafterhours@mail.nih.gov.

3. Draw required dose volume according to tumor size injection volume (see below) into a syringe that is properly labeled.

4. Administer to patient as soon as possible.

Stability at 2°C to 8°C (36^0 F to 46^0 F)			
Thawed vial stability		Prepared syringe stability	
1 x 10^6 PFU/mL	**1 x 10^8 PFU/ mL**	**1x 10^6 PFU/mL**	**1x 10^8 PFU/ mL**
12 hours (inclusive of 4 hours maximum in the syringe)	48 hours (inclusive of 8 hours maximum in syringe)	4 hours	8 hours

Stability up to 27°C (80^0 F)			
Thawed vial stability		Prepared syringe stability	
1x 10^6 PFU/mL	**1x 10^8 PFU/ mL**	**1x 10^6 PFU/mL**	**1x 10^8 PFU/mL**
4 hours (inclusive of 2 hours maximum in the syringe)	4 hours (inclusive of 4 hours maximum in the syringe)	2 hours	4 hours

3. Stability:

Shelf-life surveillance of the intact vials is on-going.

NOTE: Upon receipt of the agent supplies, the site has **90 seconds** to verify the contents and place the agent supplies in the -80° (+/- 10^0C) freezer once the inner shipping container lid is opened and the supply exposed to room temperature. See Section 18.9 and Section 18.10.

k. Drug Ordering and Accountability

1. Drug Ordering

Starter supplies will not be provided. NCI supplied agents may be requested by the responsible Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that drug be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP assigned protocol number (**S1607**) must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572, Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF) and a CV. If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution. Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

Initial agent supplies may be requested only when subject enrollment onto the study is confirmed. There will be NO next day delivery of Talimogene laherparepvec requests available. Sites must plan agent ordering and study subject treatment accordingly.

Agent order requests received on **Monday, Tuesday, or Wednesday** of the week, will be shipped on Tuesday, Wednesday and Thursday, respectively. Agent order requests received on Thursday or Friday of the week will be shipped on Monday of the following week. There will be no exceptions to this planned schedule. Sites should also consider planned Federal Government holidays when submitting agent requests and scheduling study subject treatment.

Talimogene laherparepvec will be shipped on dry ice. Only one strength of the agent will be in a single shipping container. You may receive multiple shipping containers for a single strength depending on the number vials being shipped. Upon receipt of the agent supplies, the site has 90 seconds to verify the contents and place the agent supplies in the 80^0 C (+/- 10^0 C) freezer (see Section 18.9) once the inner shipping container lid is opened

and the supply exposed to room temperature. Record exposure time in the temperature exposure tracking log (see Section 18.10). The log must be retained with your study records. If exposure time exceeds 90 seconds, quarantine the agent supplies in the 80^0 C (+/- 10^0 C) freezer and call PMB immediately at 240/276-6575 for guidance.

2. Drug Handling and Accountability (NCI logs or other)

   The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

3. Drug return and/or disposition instruction

   a. Drug disposition: All undispensed drug supplies should be returned to the PMB. When it is necessary to return study drug (e.g., sealed bottles remaining when PMB sends a stock recovery letter), investigators should return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov).

   b. Drug Expiration: Stability testing is ongoing. PMB will send a stock recovery letter when notified that the agent is no longer suitable for use.

4. Contact Information

   CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/

   NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov

   PMB policies and guidelines:
   http://ctep.cancer.gov/branches/pmb/agent_management.htm

   PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP

   CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/

   CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov

   IB Coordinator: IBCoordinator@mail.nih.gov

   PMB email: PMBAfterHours@mail.nih.gov

4.0 STAGING CRITERIA

All patients will be staged using the AJCC 7th edition, 2009

STAGE III

Any T	≥ N1	M0

Stage IV

Any T	Any N	M1

Primary Tumor (T)

TX	Primary tumor cannot be assessed (e.g., curettaged or severely regressed melanoma)
T0	No evidence of primary tumor
Tis	Melanoma in situ
T1	Melanomas 1.0 mm or less in thickness
T2	Melanomas 1.01 – 2.0 mm
T3	Melanomas 2.01 – 4.0 mm
T4	Melanomas more than 4.0 mm

Regional Lymph Nodes (N)

NX	Patients in whom the regional nodes cannot be assessed (e.g., previously removed for another reason)
N0	No regional metastases detected
N1-3	Regional metastases based upon the number of metastatic nodes and presence or absence of intralymphatic metastases (in transit or satellite metastases)

Distant Metastasis (M)

M0	No detectable evidence of distant metastases
M1a	Metastases to skin, subcutaneous or distant lymph nodes
M1b	Metastases to lung
M1c	Metastases to all other visceral sites or distant metastases to any site combined with an elevated serum LDH

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. For each criterion requiring test results and dates, please record this information on the Onstudy Form and submit via Medidata Rave® (see Section 14.0). Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at 206/652-2267 or melanomaquestion@crab.org prior to registration.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday 4 weeks later would be considered Day 28. This allows for efficient patient scheduling without exceeding the guidelines. **If Day 14, 28, 42, or 56 falls on a weekend or holiday, the limit may be extended to the next working day.**

5.1 Disease Related Criteria

a. Patients must have pathologically confirmed Stage IV or unresectable Stage III melanoma (see Section 4.0). Patients must not have disease that is suitable for local therapy, administered with curative intent.

b. Patients must have measurable disease per RECIST 1.1 (see Section 10.1). Contrast-enhanced CT scans of the chest, abdomen and pelvis are required. A whole body PET/CT scan with diagnostic quality images and intravenous iodinated contrast may be used in lieu of a contrast enhanced CT of the chest, abdomen and pelvis. Imaging of the head and neck, or the limbs is required only if the patient has a lesion(s) in these areas. Contrast may be omitted if the treating investigator believes that exposure to contrast poses an excessive risk to the patient. If skin lesions are being followed as measurable disease, photograph with a ruler included and physician's measurements, must be kept in the patients chart as source documentation. All measurable lesions must be assessed within 28 days prior to registration. Tests to assess non-measurable disease must be performed within 42 days prior to registration. All disease must be assessed and documented on the Baseline Tumor Assessment Form (RECIST 1.1).

c. Cohort A: Patients must have at least one measurable visceral lesion (per RECIST 1.1). A visceral lesion is any solid organ except for skin, lymph node, and musculoskeletal tissue. At least one of these visceral lesions must be measurable per RECIST 1.1.

Cohort B: Patients must not have any visceral lesions.

d. Patients must, in the opinion of the treating physician, be candidates for intralesional administration into cutaneous, subcutaneous, or nodal lesions.

e. Patients may have brain metastases if all lesions have been treated with stereotactic radiation therapy, craniotomy, or gamma knife therapy and have not required steroids for at least 14 days prior to registration.

5.2 Prior/Concurrent Therapy Criteria

a. Patient must have had prior treatment with anti-PD-1 or anti-PD-L1 agents and have documented disease progression on these agents prior to registration (see Section 18.1 for a list of these agents). Patients who have progressed after adjuvant anti-PD1/L1 agents are eligible.

b. Patients must not have had surgery, biologic therapy, or hormonal therapy within 14 days prior to registration. Patients must not have had chemotherapy, targeted small molecule therapy, or radiation therapy within 14 days prior to registration. Patients must not have had a monoclonal antibody for cancer treatment, except anti-PD1/L1 antibodies, within 28 days prior to registration.

- Patients must have recovered from all adverse events due to prior anti-cancer therapy (residual toxicity ≤ Grade 1) prior to registration, with the exception of patients with ≤ Grade 2 neuropathy, ≤ Grade 2 hypothyroidism, or ≤ Grade 2 alopecia.
- If patients received major surgery, they must have recovered adequately from toxicity and/or complications from the intervention prior to registration.

c. Patients must not have received prior treatment with talimogene laherparepvec (T-VEC). Prior treatment with T-VEC is defined as receiving at least one injection with 1 x 10^8 pfu.

d. Patients must not have received any live vaccine within 30 days prior to registration. Seasonal flu vaccines that do not contain live virus are permitted.

e. Patients must not be planning to receive other biologic therapy, radiation therapy, hormonal therapy, chemotherapy, surgery, or other therapy while on this protocol. Palliative radiation therapy or surgery can be considered for symptomatic non-target lesions after discussions with the study team.

5.3 Clinical/Laboratory Criteria

a. Patients must be ≥ 18 years of age.

b. Patients must have Zubrod Performance Status ≤ 2. (see Section 10.4).

c. Patients must have adequate hematologic function as evidenced by all of the following within 28 days prior to registration: ANC ≥ 1,500/mcL; hemoglobin ≥ 8 g/dL; platelets ≥ 100,000/mcL.

d. Patients must have adequate hepatic function as evidenced by all of the following within 28 days prior to registration: albumin ≥ 2.5 g/dL, total bilirubin ≤ 1.5 x Institutional Upper Limit of Normal (IULN) except patients with documented Gilbert's Syndrome (≤ 3 x IULN is eligible); AST and ALT both ≤ 3 x IULN.

e. Patients must have LDH obtained prior to registration.

f. Patients must have complete physical examination and medical history obtained within 28 days prior to registration.

g. Patients must not require use of systemic corticosteroid within 14 days prior to registration or during protocol treatment. Patients with preexisting severe autoimmune disease requiring systemic corticosteroids or ongoing immunosuppression are not eligible.

h. Patients must not have known history of hepatitis B, hepatitis C, or HIV due to contraindication of talimogene laherparepvec (T-VEC) in immune-compromised patients and that administration of talimogene laherparepvec (T-VEC) has not been tested in HIV-positive patients. The use of physiologic doses of corticosteroids may be approved after consultation with the Study Chair.

i. Patients must not have a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.

j. Patients must not have an active infection requiring systemic therapy nor a viral infection requiring intermittent treatment with an antiherpetic drug, other than intermittent topical use.

k. Patients must not have active herpetic skin lesions or prior complications of herpetic infection (e.g., herpetic keratitis or encephalitis) which requires intermittent or chronic treatment with an anti-herpetic drug other than intermittent topical use.

l. Patients must not have organ allografts.

m. Patients must not have an uncontrolled intercurrent illness or whose control may be jeopardized by the treatment with the study therapy, or psychiatric illness/social situations which would limit compliance with study requirements.

n. Patients must not have active autoimmune disease (e.g., pneumonitis, glomerulonephritis, vasculitis, or other) that requires systemic treatment (i.e., use of corticosteroids, immunosuppressive drugs or biological agents used for treatment of autoimmune diseases) in the past 2 years. Replacement therapy (e.g., thyroxine for hypothyroidism, insulin for diabetes or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment for autoimmune disease.

o. Patient must not have evidence of any clinically significant immunosuppression such as the following:

1. Primary immunodeficiency state such as Severe Combined Immunodeficiency Disease;
2. Concurrent opportunistic infection;
3. Receiving systemic immunosuppressive therapy (>2 weeks) including oral steroid doses >10 mg/day of prednisone or equivalent within 2 weeks prior to enrollment.

p. Patients must not have any other malignancy that requires active treatment.

q. Patients must not be pregnant or nursing due to risk of fetal or nursing infant harm. Women of reproductive potential must have a negative serum pregnancy test within 7 days prior to registration. Women/men of reproductive potential must have agreed to use an effective contraceptive method while on study and for 120 days after last study treatment. A woman is considered to be of "reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

5.4 Specimen Submission Criteria

Patients must be offered the opportunity to submit archival tissue for translational medicine as described in Section 15.1. Patients must also be willing to undergo biopsies and submit tissue and blood for translational medicine as described in Section 15.1. With patients consent, any remaining specimens will be banked for future use.

5.5 Regulatory Criteria

a. Patients ***must*** be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.

b. As a part of the OPEN registration process (see Sections 13.3 and 13.4 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

6.0 STRATIFICATION FACTORS

Patients will be stratified into two cohorts.

Cohort A: Patients with at least one visceral lesion (at least one must be measurable).

Cohort B: Patients with no evidence of visceral lesions.

7.0 TREATMENT PLAN

For treatment or dose modification questions, please contact Dr. Hu-Lieskovan at 801/585-0308 (or siwen.hu-lieskovan@hci.utah.edu) For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at http://swog.org (see Policy #38 under the Policies & Procedures link in the “About” dropdown).

7.1 Treatment

Patients will receive the following treatment for up to two years or until meeting one of the criteria in Section 7.4.

Agent	Dose	Route	Day	Schedule [a]
T-VEC[f]	up to 4 ml of 1 million PFU/mL [d] (10^6 PFU/mL)	Intralesional	1	Cycle 1
T-VEC[f]	up to 4 ml of 100 million PFU/mL [d] (10^8 PFU/mL)	Intralesional	1	Cycles 2-36
Pembrolizumab (MK-3475)	200 mg*	IV over 30 min [e]	1	Cycles 1-36 [c*]

[a] Note: One cycle = 21 days; Maximum of 36 cycles,
[b] All planned doses of pembrolizumab (MK-3475) must be administered. Missed doses must be made up.
[c] Please see Table 1: Injection Volume Per Lesion below.
[d] pembrolizumab (MK-3475) infusion timing should be as close to 30 minutes as possible; however, a window of -5 and +10 minutes is permitted (i.e., 25-40 minutes).
[e] pembrolizumab (MK-3475) infusion timing should be as close to 30 minutes as possible; however, a window of -5 and +10 minutes is permitted (i.e., 25-40 minutes).
[f] If patient has a confirmed complete response in the injectable lesions, as defined in section 10.3.a, with stable disease or better in all other sites of disease, contact the study chair for permission to permanently discontinue the administration of T-VEC. Patient must continue on pembrolizumab (MK-3475) per protocol.

a. Administration of talimogene laherparepvec (T-VEC)

All reasonably injectable lesions (cutaneous, subcutaneous, and nodal lesions with or without image ultrasound guidance) should be injected with the maximum dosing volume available on an individual dosing occasion. If the patient has more than one injectable lesion, one lesion must be left **un-injected** prior to the Day 28 biopsy for Cohort B (see Section 15.1) Talimogene laherparepvec (T-VEC) must

not be administered into visceral organ metastases. On each treatment day, prioritization of injections is recommended as follows:

- Any new injectable tumor that has appeared since the last injection
- By tumor size, beginning with the largest tumor
- Any previously un-injectable tumor(s) that is now injectable

Within the injection volume guidelines in the table below, it is recommended that each lesion receive the maximum amount possible at each visit before moving onto the next lesion, subject to tumor-specific limitations (such as inability to inject the full amount into the lesion). Prescribe the estimated total volume by rounding up to the nearest 1 mL.

Lesions should be injected until the maximum volume per day (4 mL) has been reached or there are no further injectable lesions, whichever comes first. The TOTAL maximum dose in any one treatment is 4 mL for all lesions combined. Use the maximum amount whenever lesions allow.

Table 1: Injection Volume Per Lesion

Tumor Size (longest dimension)	Maximum Injection Volume PER Lesion
> 5 cm	4 mL
> 2.5 cm to 5cm	2 mL
> 1.5 cm to 2.5 cm	1 mL
> 0.5 cm to 1.5 cm	0.5 mL
≤ 0.5 cm	0.1 mL

b. Injection Site Care

After administration of talimogene laherparepvec (T-VEC) the injected lesions will be covered with a watertight dressing which allows for air exchange and it may also include an absorbent pad underneath covering the lesion. These dressings are like the dressings that are placed on skin when intravenous lines are placed to deliver medicine. The dressing can be removed 7 days after the last talimogene laherparepvec (T-VEC) injection. See also Section 18.6: Instructions for talimogene laherparepvec (T-VEC) Site Care and Section 18.7: Information Related to Exposure to talimogene laherparepvec (T-VEC).

c. Administration of pembrolizumab (MK-3475)

Pembrolizumab (MK-3475) treatment will be administered on Day 1 of each 3-week treatment cycle, after all procedures and assessments have been completed. Pembrolizumab (MK-3475) treatment may be administered up to 3 days before or after the protocol-specified Q 3 weeks due to administrative reasons.

Pembrolizumab (MK-3475) will be administered as a 30 minute IV infusion. Infusion timing should be as close to 30 minutes as possible; however, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 25-40 minutes).

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Patients should be back on

study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the study chair. The reason for interruption should be documented in the patient's study record.

All planned doses must be administered. Missed doses must be made up.

7.2 Full CDUS Reporting Requirement

Because this study contains an investigational drug for which CTEP holds the IND, it falls under CTEP requirements for full reporting. This involves required submission of cycle-specific toxicity and dose information (see Section 14.4, the **S1607** Treatment Form, and the **S1607** Adverse Event Form). A cycle is defined as 21 days.

7.3 Prohibited and Cautionary Concomitant Medications

Patients should not receive the following therapies during this trial:

- Antineoplastic systemic chemotherapy or biological therapy.
- Immunotherapy not specified in this protocol.
- Any non-study anti-cancer agent (investigational or non-investigational).
- Investigational agents other than pembrolizumab (MK-3475) and talimogene laherparepvec (T-VEC).
- Radiation therapy
    - Note: Administration of palliative radiation therapy to non-targeted lesions is allowed.
- Anti-viral agents, unless approved after consultation with the study chairs.
- Live vaccines: Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, shingles, yellow fever, rabies, Bacillus Calmette-Guérin (BCG), and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Study Chairs.

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

Any steroid use other than emergency situations must be discussed with the study chair.

7.4 Criteria for Removal from Protocol Treatment

a. Completion of protocol treatment (36 cycles)

b. Progression of disease or symptomatic deterioration (as defined in Section 10.2).

1. A minority of subjects treated with immunotherapy may derive clinical benefit either delayed responses, stable disease, or increased overall survival despite initial evidence of progressive disease (PD).

Patients may be permitted to continue treatment beyond initial RECIST 1.1-defined PD as long as they meet the following criteria:

- Patients must be clinically stable with no change in performance status due to disease progression.
- No indication for immediate alternative treatment.
- Patient shows clinical benefit and tolerates study drug, as determined by the investigator. The assessment of clinical benefit should take into account whether the subject is clinically stable or deteriorating and likely or unlikely to receive further benefit from continued treatment.
- The time of progression is noted from the first assessment that meets criteria as defined in Section 10.2d

Note: Patients who continue beyond initial RECIST-defined PD must have repeat scans every12 weeks to ensure that treatment continuation criteria are still met.

c. Unacceptable toxicity.

d. T-VEC treatment delay > 12 weeks for any reason other than a confirmed CR in the injectable lesions.

e. Positive pregnancy test.

f. The patient may withdraw from the study at any time for any reason.

7.5 Discontinuation of Treatment

All reasons for discontinuation of treatment must be documented in the Off Treatment Notice.

7.6 Follow-Up Period

All patients will be followed, as indicated in Section 9.0, until 5 years after registration or death, whichever occurs first. Subsequently, patients will be asked to provide contact information for survival status follow-up (via phone) until 10 years after registration, for compliance with NIH OSP guidelines for long-term follow-up.

8.0 TOXICITIES TO BE MONITORED AND DOSE MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events

Two different versions of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be used on this study.

a. Serious Adverse Event (SAE) reporting

The CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 will be utilized **for SAE reporting only**. The CTCAE Version 5.0 can be downloaded from the CTEP home page (https://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 5.0.

b. Routine toxicity reporting

This study will utilize the CTCAE Version 4.0 for routine toxicity reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP home page (https://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0.

8.2 Dose Modifications

a. General Pembrolizumab (MK-3475) Dose Modifications

1. Missed doses of pembrolizumab (MK-3475) must be made up.

2. Adverse events (both non-serious and serious) associated with pembrolizumab (MK-3475) 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 (MK-3475) must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 1 below. See Section 8.2b for supportive care guidelines, including use of corticosteroids.

3. If pembrolizumab (MK-3475) must be permanently discontinued, patient may continue to receive talimogene laherparepvec (T-VEC).

NOTE: Due to the possible effect of treatment with pembrolizumab (MK-3475) on the immunologic response to infectious disease vaccines, patients must not have had any infectious disease vaccination (e.g., standard influenza, H1N1 influenza, pneumococcal, meningiococcal, tetanus toxoid) 1 week before or after any dose of pembrolizumab (MK-3475).

Table 1 Dose Modification Guidelines for Drug-Related Adverse Events related to pembrolizumab (MK-3475)

General instructions:
1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembrolizumab must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last pembrolizumab treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If pembrolizumab has been withheld, pembrolizumab may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab	Corticosteroid and/or other therapies	Monitoring and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of	• Monitor participants for signs and

	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue	1 - 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AST or ALT elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 - 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypothyroidism	Grade 2, 3, 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 – 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		

Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All Other immune-related AEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

[a] AST/ALT: >3.0 - 5.0 x ULN if baseline normal; >3.0 - 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 - 3.0 x ULN if baseline normal; >1.5 - 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 - 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 - 10.0 x ULN if baseline normal; >3.0 - 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.

[e] Events that require discontinuation include but are not limited to: Guillain-Barre Syndrome, encephalitis, Stevens-Johnson Syndrome and toxic epidermal necrolysis.

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

b. Talimogene laherparepvec (T-VEC) Dose Delay and Treatment Discontinuation Guidelines **AEs that are considered "Dose Limiting" for talimogene laherparepvec (T-VEC)** Treatment Modification Guidelines

1. Herpetic events that should be considered DLTs:
   - Serious herpetic events such as herpetic encephalitis, encephalomyelitis or disseminated herpetic infection.
   - Any herpetic events confirmed due to talimogene laherparepvec (T-VEC) that require treatment with acyclovir or similar anti-viral agent.

   Talimogene laherparepvec (T-VEC) treatment should be held if systemic acyclovir or other anti-viral is indicated. If ongoing anti-viral treatment is required, talimogene laherparepvec (T-VEC) treatment should be permanently discontinued.

   * Herpetic events due to wild-type HSV-1 or wild-type HSV-2 which require acyclovir and are not due to talimogene laherparepvec (T-VEC) (as confirmed by PCR testing) should not

be considered as DLTs caused by talimogene laherparepvec (T-VEC).

2. DLT will also be defined as any of the following talimogene laherparepvec (T-VEC)-related toxicity:
    - Grade 3 or greater immune-mediated AEs.
    - Grade 3 or greater allergic reactions.
    - Any grade plasmacytoma
    - Any other Grade 3 or greater hematologic or non-hematologic toxicity, with the exceptions of:
        - Any grade of alopecia,
    - Grade 3 arthralgia or myalgia,
    - Grade 3 fatigue, that improved to Grade 0-1 within 2 cycles,
    - Grade 3 fever,
    - Grade 3 diarrhea or vomiting responding to supportive care.

Dose Reductions/delay:

- Dose reductions with regards to changes in the concentrations of talimogene laherparepvec (T-VEC) are not permitted. However, patients may require a reduction in the volume injected due to a disease response (defined in dosing Section 7.1a) or due to local toxicity at the injection site.
- If talimogene laherparepvec (T-VEC) treatment was delayed due to AEs or other reasons by >1 week, that dose will be deemed to have been missed and the patient will proceed to the next scheduled treatment visit.
- If DLTs occur, talimogene laherparepvec (T-VEC) administration should be delayed until the DLT has resolved to at least CTCAE version 4.0 Grade 1. (AEs less than DLT may also require talimogene laherparepvec (T-VEC) dose delay. See instructions in Table 2 below)
- If talimogene laherparepvec (T-VEC) dosing is delayed by more than 4 weeks (approximately 7 weeks from the previous dose) due to treatment related AEs, talimogene laherparepvec (T-VEC) should be permanently discontinued.
- If talimogene laherparepvec (T-VEC) dosing is delayed by more than 4 weeks (approximately 7 weeks from the previous dose) for reasons other than treatment-related toxicity, the case must be reviewed by the sponsor of the study (CTEP) to determine if the patient can resume talimogene laherparepvec (T-VEC) therapy.
- If talimogene laherparepvec (T-VEC) has to be permanently discontinued for any reason other than a complete response, patient will be removed from further treatment with pembrolizumab (MK-3475) and will come off study.

Table 2: Treatment delays and discontinuation due to Specific AEs related to T-VEC		
Condition	**Grade**	**Talimogene laherparepvec (T-VEC) modification**
• Injection site reactions	Any grade	Volume of talimogene laherparepvec (T-VEC) injection may be adjusted and should be held based on the degree of local toxicities
• Active herpetic cutaneous or mucosal lesions, herpes labialis, or active dermatoses in the region of the injected tumors	Any grade	Mild: continue talimogene laherparepvec (T-VEC) If requiring systemic acyclovir or similar anti-viral agents: Hold talimogene laherparepvec (T-VEC).
• Serious herpetic events such as herpetic encephalitis, encephalomyelitis or disseminated herpetic infection	Any grade	Discontinue talimogene laherparepvec (T-VEC)
• Any condition requiring corticosteroid dosing of >10 mg prednisone daily (or equivalent) and/or other immunosuppressive medication for related toxicities	N/A	Hold talimogene laherparepvec (T-VEC) dosing until corticosteroid dose has decreased to <10 mg prednisone daily (or equivalent) and the other immunosuppressive medication has been stopped.
• Plasmacytoma	Any grade	Permanently discontinue talimogene laherparepvec (T-VEC)
• Immune-mediated AEs (These may include pauci-immune glomerulonephritis, vasculitis, and pneumonitis, but may involve any organ system)	Grade 2 or greater	Hold talimogene laherparepvec (T-VEC) (with the exception of vitiligo). If delay is > 12 weeks, discontinue talimogene laherparepvec (T-VEC)
• Allergic reactions, or urticaria	Grade 2 or greater	Hold talimogene laherparepvec (T-VEC). If delay is > 12 weeks, permanently discontinue talimogene laherparepvec (T-VEC)
• Other talimogene laherparepvec (T-VEC) related grade 3+ AEs or intolerable grade 2 AEs (Except brief grade 3 fever, fatigue, pain, or nausea/vomiting responding to supportive care)		Hold talimogene laherparepvec (T-VEC) until AE is grade 0-1. • If delay is > 12 weeks, discontinue talimogene laherparepvec (T-VEC) • If the AE was grade 4, decision to resume talimogene laherparepvec (T-VEC) upon recovery should be reviewed with the sponsor (CTEP)

c. Concomitant Medication/Supportive Care Guidelines for pembrolizumab (MK-3475).

Medications or vaccinations specifically prohibited in Section 5.2 (eligibility criteria) are not allowed during the ongoing trial).

Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab (MK-3475).

Note: If after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below). Refer to Section 8.2a for dose modifications.

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

1. **Pneumonitis**:
   - For **Grade 2 events**:
     - Treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
   - For **Grade 3-4 events**:
     - Immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
     - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

2. **Diarrhea/Colitis**:

   Patients 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 patients 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 - 3 diarrhea/colitis:**
     - Administer oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks
   - For Grade **4 diarrhea/colitis:**
     - Treat with intravenous steroids followed by high dose oral steroids.

- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

3. **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** (onset) or **Grade 3-4** hyperglycemia
     - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
     - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

4. **Hypophysitis**:
   - **For Grade 2 events**:
     - Treat with corticosteroids.
     - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
   - For **Grade 3-4 events**:
     - Treat with an initial dose of IV corticosteroids followed by oral corticosteroids.
     - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

5. **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 hyper**thyroidism events (and **Grade 2-4** hypothyroidism):
     - In hyperthyroidism, treatment with non-selective beta-blockers (e.g. propranolol) is suggested as initial therapy.
     - In hypothyroidism, treat with thyroid hormone replacement therapy (levothyroxine or liothyroinine) as indicated per standard of care.

   - **Grade 3-4 hyper**thyroidism
     - 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.

6. **Hepatic**:
   - For **Grade 2** events:
     - Monitor liver function tests more frequently until returned to baseline values (consider weekly).
     - Treat with IV or oral corticosteroids.
   - For **Grade 3-4 events**:
     - Treat with intravenous corticosteroids for 24 to 48 hours.

- When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

7. **Renal Failure or Nephritis**:
   - For Grade 2 events, treat with corticosteroids.
   - For **Grade 3-4** events, treat with systemic corticosteroids.
     - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

8. **Skin-only Toxicity**:
   - 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.

9. **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 Infusion Reaction Treatment Guidelines below shows treatment guidelines for patients who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

d. **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 patient is deemed medically stable in the opinion of the investigator.	None

Grade 2
Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hrs
	• **Stop Infusion and monitor symptoms.**
	• Additional appropriate medical therapy may include but is not limited to:
	  ○ IV fluids
	  ○ Antihistamines
	  ○ NSAIDS
	  ○ Acetaminophen
	  ○ Narcotics
	• Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator.
	• If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 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.
		Patient may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with:
		
		Diphenhydramine 50 mg PO (or equivalent dose of antihistamine).
		
		Acetaminophen 500-1000 mg PO (or equivalent dose of antipyretic).

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
	Please Note: Prior to re-starting the infusion, confirm that the 4-hour room temperature stability from the time of the IV bag preparation will not be exceeded. Otherwise, dosing will be held until symptoms resolve and the patient should be premedicated for the next scheduled dose. **Patients who develop Grade 2 toxicity upon re-challenge, despite adequate premedication, must be permanently discontinued from protocol treatment.**	
<u>Grades 3 or 4</u> Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** • Additional appropriate medical therapy may include but is not limited to: o IV fluids o Antihistamines o NSAIDS o Acetaminophen o Narcotics o Oxygen o Pressors o Corticosteroids o Epinephrine • Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. • Hospitalization may be indicated. • **Patient is permanently discontinued from protocol treatment.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

e. Concomitant Medication Considerations for talimogene laherparepvec (T-VEC)

Talimogene laherparepvec (T-VEC) is sensitive to acyclovir and other antiherpetic viral drugs and would be rendered ineffective. Thus, if systemic anti-herpetic medication is indicated, talimogene laherparepvec (T-VEC) must be discontinued.

8.3 White blood Cell Growth Factors

If used, white blood cell growth factors, including biosimilars, must be used per ASCO guidelines (http://jco.ascopubs.org/content/24/19/3187.full) and NCCN Guidelines® Myeloid Growth Factors (http://www.nccn.org/professionals/physician_gls/pdf/myeloid_growth.pdf).

8.4 Dose Modification Contacts

For treatment or dose modification questions, please contact Dr. Hu-Lieskovan at 801/585-0308 (or Siwen.Hu-Lieskovan@hci.utah.edu) or Dr. Ribas at 310/206-3928.

8.5 Adverse Event Reporting

Toxicities (including suspected reactions) that meet the expedited reporting criteria as outlined in Section 16.0 of the protocol must be reported to the Operations Office, Study Chair and NCI via CTEP-AERS, and to the IRB per local IRB requirements.

9.0 STUDY CALENDAR

		Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6-36 [f]					
REQUIRED STUDIES **PHYSICAL** [a]	Pre Study	W 1	W 2	W 3	W 4	W 5	W 6	W 7	W 8	W 9	W 10	W 11	W 12	W 13	W 14	W 15	W 16	W 17	W 18	At Prog	Pre-Prog Off Treat F/U	Post-Prog Off Treat F/U [g]
History & Physical (w/ BSA, BP, Height & Weight) [b]	X	X			X			X			X			X			X			X	X	X
PS & Toxicity Notation	X	X			X			X			X			X			X			X	X	
Disease Assessment	X									X				X[d]						X	X	
Baseline Abnormalities	X																					
Skin Exam	X									X				X[d]								
LABORATORY [a]																						
ANC, hemoglobin, platelets	X	X			X			X			X			X			X			X		
CBC, Na, K, CO_3, BUN, Ca, fasting glucose, alkaline phosphatase, albumin	X	X			X			X			X			X			X			X		
Total and direct bilirubin [J]	X	X			X			X			X			X			X			X		
AST and ALT	X	X			X			X			X			X			X			X		
Serum Creatinine	X	X			X			X			X			X			X			X		
LDH	X	X			X			X			X			X			X			X		
TFTs (TSH, totalT3, free T4) [h]	X				X						X									X		
Pregnancy Test [c]	X	X			X			X			X			X			X			X		X

Calendar continued on next page. Click here for Footnotes.

		Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6-36 [f]					
	Pre-Study	W 1	W 2	W 3	W 4	W 5	W 6	W 7	W 8	W 9	W 10	W 11	W 12	W 13	W 14	W 15	W 16	W 17	W 18	At Prog	Pre-Prog Off Treat F/U	Post-Prog Off Treat F/U [g]
X-RAYS AND SCANS																						
Tumor Measurements (CT/MRI) [d]	X									X				X[d]						X	X	
SPECIMENS																						
Tissue biopsy [e]	X				X															X		
Archival tissue [i]	x																					
Blood Specimen Submission (20 ml) [e]	X		X		X						X									X		
TREATMENT																						
Talimogene laherparepvec (T-VEC)		X			X			X			X			X			X					
Pembrolizumab (MK-3475)		X			X			X			X			X			X					

Click here for Footnotes.

NOTE: Forms are found on the protocol abstract page on the SWOG website (www.swog.org). Forms submission guidelines are found in Section 14.0.

NOTE: Unless indicated otherwise in the protocol, scheduled procedures and assessments (treatment administration, toxicity assessment for continuous treatment, disease assessment, specimen collection, and follow-up activities) must follow the established SWOG guidelines as outlined in https://www.swog.org/sites/default/files/docs/2017-10/Best%20Practices%20upddate.pdf.

FOOTNOTES:

a The following exams & labs are performed prior to receiving first dose & prior to all other infusions until end of protocol treatment: physical (w/BSA, BP, & WT), performance status (PS), toxicity notation, ANC, hemoglobin, platelets, total and direct bilirubin, AST and ALT, serum creatinine, fasting glucose, LDH, alkaline phosphatase, albumin. The following are recommended for good medical practice: CBC, Na, K, CO_3, BUN, and Ca. Adverse Event Assessments on the study will continue for all patients until resolution of adverse effects. Patients with ongoing toxicities should be seen more often as clinically indicated.

b History prior to each treatment initiation to include a menstrual, sexual, and contraceptive use history, including date of last menstrual period (for women of childbearing potential) which will help determine the need for pregnancy testing. Similar questions regarding contraceptive use to be asked of men who are sexually active with women of childbearing potential.

c Women of child bearing potential must have a negative serum or urine pregnancy test at screening within 7 days prior to registration. Following registration, serum or urine pregnancy tests are required within 72 hours prior to the first dose of study treatment, then according to institutional practice during therapy, tests should coincide with clinic visits for blood work and ending with discontinuation of study treatment. At discontinuation, a negative pregnancy test within the preceding 6 weeks is sufficient. A pregnancy test should be done at any time there are clinical concerns for possible pregnancy.

d Disease assessments by CT, MRI, or skin measurement will be performed initially at weeks 9 (+/- 1 week) followed by confirmatory scan/skin measurement at week 13 (+/- 1 week), thereafter every 12 weeks (+/- 2 weeks) until disease progression. Patients who remain on protocol treatment following initial disease progression (see Section 7.4b) must continue this same disease assessment schedule until removal from protocol treatment. The same measurement modality as used at pre-study for disease assessment must be used throughout the trial.

e See Section 15.1 for additional information. To be performed on or prior to Day 1 and on Day 21-35 (Day 28 +/- 7 days). If it is not feasible to obtain the first biopsy, tissue that was collected at any timepoint since demonstrated progression on PD-1 or PD-L1 therapy may be substituted provided that at least 20 unstained slides are available. NOTE: If any blood collection timepoint was missed, sites must draw blood at the next patient visit for lab work.

f Protocol treatment and parameters will continue at these intervals for 36 cycles of treatment until progression of disease or until patient has met any of the guidelines in Section 7.4. Patients who progress but meet the criteria in section 7.4.b.1 for staying on protocol treatment for clinical benefit should continue follow-up as indicated by this column.

g Follow-up visits should occur at least every 6 months (+/- 1 week) through 1 year after completion of treatment and then annually (+/- 1 month) until 5 years from registration or death (whichever occurs first).

h Patients must be monitored for changes in thyroid function and for clinical signs/symptoms of thyroid disorders (as clinically indicated)

I Collected prior to previous anti-PD-1 or anti-PD-L1 treatment.

J To be performed as clinically indicated.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT ANALYSIS

10.1 Measurability of Lesions

a. **Measurable disease:** Measurable disease is defined differently for lymph nodes compared with other disease and will be addressed in a separate section below.

1. Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 2.0 cm by chest x-ray, by ≥ 1.0 cm with CT or MRI scans, or ≥ 1.0 cm with calipers by clinical exam. All tumor measurements must be recorded in decimal fractions of centimeters (or millimeters).

   The defined measurability of lesions on CT scan is based on the assumption that CT slice thickness is 0.5 cm or less. If CT scans have slice thickness greater than 0.5 cm, the minimum size for a measurable lesion should be twice the slice thickness.

2. Malignant lymph nodes are to be considered pathologically enlarged and measurable if it measures ≥ 1.5 cm in **SHORT AXIS** (greatest diameter perpendicular to the long axis of the lymph node) when assessed by scan (CT scan slice recommended being no greater than 0.5 cm).

b. **Non-measurable disease**: All other lesions (or sites of disease), including small lesions (longest diameter < 1.0 cm or pathologic lymph nodes with ≥ 1.0 cm to < 1.5 cm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered non-measurable as are previously radiated lesions that have not progressed

c. Notes on measurability

1. For CT and MRIs, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should by performed with breath-hold scanning techniques, if possible.

2. PET-CT: At present, the low dose or attenuation correction CT portion of a PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT, then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT.

3. Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

4. Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition simple cysts.

5. If a target lesion becomes very small some radiologists indicate that it is too small to measure. If the lesion is actually still present, a default measurement of 0.5 cm should be applied. If the radiologist believes the lesion has gone, a default measurement of 0.0cm should be recorded.

10.2 Objective Status at Each Disease Evaluation

Objective Status is to be recorded at each evaluation. All measurable lesions up to a maximum of 2 lesions per organ 5 lesions in total, representative of all involved organs, should be identified as ***target*** lesions at baseline. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as ***non-target*** lesions. Measurements must be provided for target measurable lesions, while presence or absence must be noted for non-target measurable and non-measurable disease.

For studies that use disease progression as an endpoint, whole body scanning at specific intervals is necessary to determine that progression is NOT present outside of the "target" areas. Therefore, in these studies it is not acceptable to image only the "target" areas of the body in follow-up scans. For study-specific imaging requirements, see the Study Calendar in Section 9.0.

a. **Complete Response (CR):** Complete disappearance of all target and non-target lesions (with the exception of lymph nodes mentioned below). No new lesions. No disease related symptoms. Any lymph nodes (whether target or non-target) must have reduction in short axis to < 1.0 cm. All disease must be assessed using the same technique as baseline.

b. **Partial Response (PR)**: Applies only to patients with at least one measurable lesion. Greater than or equal to 30% decrease under baseline of the sum of appropriate diameters of all target measurable lesions. No unequivocal progression of non-measurable disease. No new lesions. All target measurable lesions must be assessed using the same techniques as baseline.

c. **Stable**: Does not qualify for CR, PR, Progression or Symptomatic Deterioration. All target measurable lesions must be assessed using the same techniques as baseline.

d. **Progression**: One or more of the following must occur: 20% increase in the sum of appropriate diameters of target measurable lesions over smallest sum observed (over baseline if no decrease during therapy) using the same techniques as baseline, as well as an absolute increase of at least 0.5 cm. Unequivocal progression of non-measurable disease in the opinion of the treating physician (an explanation must be provided). Appearance of any new lesion/site. Death due to disease without prior documentation of progression and without symptomatic deterioration (see Section 10.2e).

NOTE: Any initial documentation of progression at the Week 9 assessment (or earlier) must be confirmed by a second determination of progression at the Week 13 assessment. If the Week 13 assessment documents an absence of progression, the patient's disease is assumed not to have progressed. If the Week 13 assessment is inadequate and there are no subsequent assessments documenting absence of progression, the initial documentation of progression will be considered definitive. After the disease assessment at Week 13, the documentation of any of the criteria in the paragraph above will be counted as disease progression.

Notes regarding new lesions: FDG-PET imaging can complement regular scans in identifying new lesions according to the following algorithm.

1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of progression based on a new lesion.

2. No FDG-PET at baseline and a positive FDG-PET at follow-up corresponding to a potential new site of disease must have a confirmation by anatomical assessment (e.g., CT, MRI, x-ray) as new site of disease to be considered progressive disease. In such a case, the date of progressive disease will be the date of the initial abnormal FDG-PET.

e. **Symptomatic deterioration:** Global deterioration of health status requiring discontinuation of treatment without objective evidence of progression. Efforts should be made to obtain objective evidence of progression after discontinuation.

f. **Assessment inadequate, objective status unknown.** Progression or symptomatic deterioration has not been documented, and one or more target measurable lesions have not been assessed or inconsistent assessment methods were used.

g. Objective status notes:

1. Non-measurable and non-target measurable disease do not affect Objective Status in determination of CR (must be absent--a patient who otherwise has a CR, but who has non-measurable or non-target measurable disease present or not assessed, will be classified as having a PR). However, non-measurable and non-target lesions are included in determination of progression (if new sites of disease develop or if unequivocal progression occurs in the opinion of the treating physician).

2. An objective status of PR or stable cannot follow one of CR. Stable can follow PR only in the rare case that tumor increases too little to qualify as progression, but enough that a previously documented 30% decrease no longer holds.

3. In cases for which initial flare reaction is possible (hypercalcemia, increased bone pain, erythema of skin lesions), objective status is not progression unless either symptoms persist beyond 4 weeks or there is additional evidence of progression.

4. Lesions that appear to increase in size due to presence of necrotic tissue will not be considered to have progressed.

5. For bone disease documented on bone scan only, increased uptake does not constitute unequivocal progression. However, increase in the soft tissue component of a lesion as measured by CT or MRI would constitute progression.

6. Appearance of new pleural effusions does not constitute unequivocal progression unless cytologically proven of neoplastic origin, since some effusions are a toxicity related to therapy or other medical conditions. Increase in the size of an existing effusion does not constitute unequivocal progression, since the fluid status of the patient could alter the size of the effusion.

7. If CR determination depends on a lesion for which the status is unclear by the required tests, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate.

10.3 Best Response

This is calculated from the sequence of objective statuses. Best response should be documented for as long as the patient remains on protocol treatment.

a. CR: Two or more consecutive objective statuses of CR a minimum of four weeks apart.

b. PR: Two or more consecutive objective statuses of PR or better a minimum of four weeks apart but not qualifying as CR.

c. Unconfirmed CR: One objective status of CR but not qualifying as CR or PR.

d. Unconfirmed PR: One objective status of PR but not qualifying as CR, PR or unconfirmed CR.

e. Stable/no response: At least one objective status of stable/no response documented at least 6 weeks after registration, but not qualifying as anything else above.

f. Increasing disease: Objective status of progression within 13 weeks of registration, not qualifying as anything else above.

g. Symptomatic deterioration: Objective status of symptomatic deterioration within 13 weeks of registration, not qualifying as anything else above.

Inadequate assessment, response unknown: Progression or symptomatic deterioration greater than 13 weeks after registration and no other response category applies.

10.4 Performance Status

Patients will be graded according to the Zubrod Performance Status Scale.

POINT	**DESCRIPTION**
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

10.5 Progression-Free Survival

From date of registration to date of first documentation of progression (see note in Section 10.2d), or death due to any cause. Patients last known to be alive without report of progression are censored at date of last contact.

10.6 Time to Death

From date of registration to date of death due to any cause. Patients last known to be alive are censored at date of last contact.

10.7 Durable Response Rate

Complete or partial response per RECIST 1.1 with no evidence of disease progression for at least 180 days from the initial documentation of CR/PR. Patients last known to have an objective response but who are lost to follow-up before 180 days will be considered to have inadequate disease assessments. Patients known to have an objective response who have an objective response at the following disease assessment will be considered to have continued objective response in the interim, regardless of duration between disease assessments.

10.8 Response in the Injected Lesions

Best response of CR, UCR, PR or UPR as specified in Section 10.3 taking into consideration only lesions deemed injectable at any time prior to progression as defined in Section 10.2d. All other disease must be stable or better. No new visceral or otherwise uninjectable lesions.

10.9 Response in visceral lesions

Best response of CR, UCR, PR or UPR as specified in Section 10.3 taking into consideration only visceral lesions present at baseline. All other disease must be stable or better. No new lesions.

10.10 Response in non-injected (non-visceral) lesions

Best response of CR, UCR, PR or UPR as specified in Section 10.3 taking into consideration only lesions that were not injected at Cycle 1, Week 1. All other disease must be stable or better. No new lesions.

11.0 STATISTICAL CONSIDERATIONS

11.1 Cohort A: Patients who have injectable lesions and measurable visceral diseases

a. Cohort A will use a 2-stage design with an accrual goal of 17 eligible patients in total. This includes 9 eligible patients in the first stage and 8 eligible patients in the second stage. The anticipated accrual rate for Cohort A is 1 patient per month. Assuming an ineligibility rate of 10%, we will accrue 19 total patients (10 patients in the first stage and 9 patients in the second stage) to enroll 17 eligible patients.

b. Primary Endpoint: The primary endpoint for Cohort A is objective response (confirmed CR or PR) rate (ORR).

We propose a two-stage design with the assumption that a true ORR of 5% or lower indicates that the treatment will not be of further interest and that a true ORR of 25% or more would be of considerable interest. The alternative hypothesis of

25% ORR is what is felt to be a clinically significant antitumor activity of adding talimogene laherparepvec (T-VEC) to anti-PD-1 for a population of patients who are already progressing on prior anti-PD-1 therapy.

Initially, 9 eligible patients would be entered. If necessary, Cohort A may be temporarily closed to accrual while the data mature. If zero objective responses (confirmed PR/CR) are observed among these 9 patients, then Cohort A would be closed and the treatment determined to be inactive in this population. If one or more objective responses (confirmed PR/CR) are observed, then 8 more eligible patients would be accrued, for a total sample size of 17 eligible patients. Two or more objective responses (confirmed PR/CR) out of 17 patients would be considered evidence that the treatment warrants further study, provided other factors such as toxicity and overall survival also appear favorable. This design has an alpha of 17.2% (i.e. probability of declaring the regimen warrants further study when the true ORR is 5%) and a power of 90.2% (probability of declaring the regimen warrants further study when the true ORR is 25%).

c. Secondary Endpoints:

We will estimate the durable response rate. For Cohort A, with a total of 17 eligible patients, we will be able to estimate the durable response rate to within 23.7% (95% CI).

We will estimate the response rate (complete and partial, confirmed and unconfirmed responses) by three different methods. RECIST 1.1 will be applied, but with the following restrictions: 1) considering only the injected lesions as target lesions, 2) considering only the non-injected lesions as target lesions,3) considering only the visceral lesions as target lesions and 4) across all lesions per RECIST guidelines. We will construct 95% confidence intervals for the estimated rates. For Cohort A, with a total of 17 eligible patients, assuming all 17 patients have both injected and non-injected measurable lesions, we will be able to estimate each of these response rates to within 23.7% (95% CI).

We will estimate the median PFS and median OS and construct 95% Brookmeyer-Crowley Confidence intervals. For Cohort A, with a total of 17 eligible patients, we will be able to estimate the PFS, OS, and DR rates at a particular time point (e.g., 6 months) to within 23.7% (95% CI).

To assess the association between objective response rate and CD8 T-cell infiltration in the injected tumors, we will use a two-sample t-test to test for difference in mean quantitative CD8 expression between patients who have an objective response and patients who do not have an objective response. We will control the type I error at the two-sided 0.05 level. For Cohort A, assuming 17 eligible patients and an ORR of 25%, then we anticipate 80% power to detect a mean difference in CD8 expression of 1.68 standard deviations. If the distributions are far from normal or subject to influential points, then instead of t-tests, we will use robust, rank based or non-parametric alternatives such as the Wilcoxon test. We will repeat the analysis to assess the association between durable response rate and CD8 T-cell infiltration in the non-injected tumors.

We will assess whether ctDNA fraction at baseline and Day 28 is associated with ORR using a two-sample t-test at the two-sided 0.05 level. For Cohort A, with 17 eligible patients and assuming 25% of patients have a response, we anticipate 80% power to detect a difference in mean ctDNA fraction of 1.68 standard deviations.

11.2 Cohort B: Patients who have injectable lesions and no visceral lesions

a. Cohort B will use a 2-stage design with an accrual goal of 25 eligible patients in total. This includes 16 patients in the first stage and 9 patients in the second stage. Assuming an ineligibility rate of 10%, we will accrue 28 total patients to enroll 25 eligible patients.

b. Primary Endpoint:

The primary endpoint for Cohort B is objective response (confirmed PR or CR) rate (ORR).

We propose a two-stage design with the assumption that a true ORR of 10% or lower indicates that the treatment will not be of further interest and that a true ORR of 30% or more would be of considerable interest. The alternative hypothesis of 30% ORR is what is felt to be a clinically significant antitumor activity of adding talimogene laherparepvec (T-VEC) to anti-PD-1 for a population of patients who are already progressing on prior anti-PD-1 therapy.

Initially, 16 patients would be entered. Cohort B may be temporarily closed to accrual while the data mature. If one or fewer objective responses (confirmed PR/CR) are observed among these 16 patients, then cohort B would be closed and the treatment determined to be inactive in this population. If two or more objective responses (confirmed PR/CR) are observed, then 9 more patients would be accrued, for a total sample size of 25 patients.

Five or more objective responses out of 25 eligible patients would be considered evidence that the treatment warrants further study, provided other factors such as toxicity and overall survival also appear favorable. This design has an alpha of 10% (i.e. probability of declaring the regimen warrants further study when the true ORR is 10%) and a power of 90% (probability of declaring the regimen warrants further study when the true ORR is 30%).

c. Secondary Objectives:

We will estimate the durable response rate. For Cohort B, with a total of 25 eligible patients, we will be able to estimate the durable response rate to within 19.6% (95% CI).

We will estimate the ORR, in injected lesions, in non-injected lesions, across all lesions and construct 95% confidence intervals for the estimated rates. For Cohort B, with a total of 25 eligible patients, we will be able to estimate the ORR in injected lesions, in non-injected lesions, across all lesions to within 19.6%.

We will estimate the median PFS and median OS and construct 95% Brookmeyer-Crowley Confidence intervals. For Cohort B, with a total of 25 eligible patients, we will be able to estimate the PFS, OS, and DR rates at a particular time point to within 19.6% (95% CI).

To assess the association between objective response rate and CD8 T-cell infiltration in the injected tumors, we will use a two-sample t-test to test for difference in mean quantitative CD8 expression between patients who have a objective response and patients who do not have an objective response. We will control the type I error at the two-sided 0.05 level. For Cohort B, assuming 25 eligible patients and a ORR of 30%, then we anticipate 80% power to detect a mean difference in CD8 expression of 1.28 standard deviations. If the distributions are far from normal or subject to influential points, then instead of t-tests, we will use robust, rank based or non-parametric alternatives such as the Wilcoxon test.

We will repeat the analysis to assess the association between durable response rate and CD8 T-cell infiltration in the non-injected tumor.

We will assess whether ctDNA fraction at baseline and Day 28 is associated with ORR using a two-sample t-test at the two-sided 0.05 level. For Cohort B, with 25 eligible patients and assuming 30% of patients have a response, we anticipate 80% power to detect a difference in mean ctDNA fraction of 1.28 standard deviations.

11.3 Data and Safety Monitoring

There is no formal data and safety monitoring committee for single arm Phase II studies. Toxicity and accrual monitoring are done routinely by the Study Chair, study Statistician and the Disease Committee Chair. Endpoint monitoring is done by the study Statistician and Study Coordinator. Accrual reports are generated weekly and formal toxicity reports are generated every 6 months. In addition, the Statistical Center, Adverse Event Coordinator at the Operations Office, SAE Physician Reviewer, and Study Coordinator monitor toxicities on an ongoing basis.

12.0 DISCIPLINE REVIEW

Discipline review is not necessary for this study.

13.0 REGISTRATION GUIDELINES

13.1 Registration Timing

Patients must be registered prior to initiation of treatment (no more than 7 calendar days prior to planned start of treatment).

13.2 Investigator/Site Registration

For patient enrollment at participating sites: Local Institutional Biosafety Committee (IBC) approval is required before a site can enroll patients to T-VEC protocols.

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet to CTEP.

a. CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed ***Statement of Investigator Form*** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed ***Supplemental Investigator Data Form*** (IDF)
- a completed ***Financial Disclosure Form*** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at http://ctep.cancer.gov/investigatorResources/investigator_registration.htm.

For questions, please contact the ***CTEP Investigator Registration Help Desk*** by email at pmbregpend@ctep.nci.nih.gov.

b. CTEP Associate Registration Procedures

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at http://ctep.cancer.gov/branches/pmb/associate_registration.htm. For questions, please contact the ***CTEP Associate Registration Help Desk*** by email at ctepreghelp@ctep.nci.nih.gov.

c. CTSU Registration Procedures
This study is supported by the NCI Cancer Trials Support Unit (CTSU).

1. IRB Approval:

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to: an active Federal Wide Assurance (FWA) number, an active roster affiliation with the Lead Network or a participating organization, a valid IRB approval, and compliance with all protocol specific requirements.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform

the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

2. Downloading Site Registration Documents:

Site registration forms may be downloaded from the **S1607** protocol page located on the CTSU members' website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the SWOG link to expand, then select trial protocol **S1607**
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

3. Requirements For **S1607** Site Registration:

- CTSU Transmittal Sheet (optional)
- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

Special Protocol Specific Requirements (PSRs) for protocols utilizing T-VEC:

- *For patient enrollment at protocol initiation:* The Principle Investigator should submit a document confirming Approval from the local Institutional Biosafety Committee (IBC) at the initial site (PI's or the coordinating site)
- *For patient enrollment at additional participating sites*: Local IBC approval is required before members site can enroll patients to T-VEC protocols.
- Additional information can be found in protocol appendix Section 18.3.

4. Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

ONLINE:	www.ctsu.org (members' section) → Regulatory Submission Portal
EMAIL:	CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)
FAX:	215/569-0206
MAIL:	CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103

5. Checking Your Site's Registration Status:

You can verify your site registration status on the members' section of the CTSU website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

13.3 OPEN Registration Requirements

The individual registering the patient must have completed the appropriate SWOG Registration Worksheet. The completed form must be referred to during the registration but should not be submitted as part of the patient data.

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at https://ctepcore.nci.nih.gov/iam/) and a 'Registrar' role on either the LPO or participating organization roster.

OPEN will also ask additional questions that are not present on the SWOG Registration Worksheet. The individual registering the patient must be prepared to provide answers to the following questions:

a. Institution CTEP ID

b. Protocol Number

c. Registration Step

d. Treating Investigator

e. Credit Investigator

f. Patient Initials

g. Patient's Date of Birth

h. Patient SSN (SSN is desired, but optional. Do not enter invalid numbers.)

i. Country of Residence

j. ZIP Code

k. Gender (select one):
- Female Gender
- Male Gender

l. Ethnicity (select one):
- Hispanic or Latino
- Not Hispanic or Latino
- Unknown

m. Method of Payment (select one):
- Private Insurance
- Medicare
- Medicare and Private Insurance
- Medicaid
- Medicaid and Medicare
- Military or Veterans Sponsored NOS
- Military Sponsored (Including Champus & Tricare)
- Veterans Sponsored
- Self Pay (No Insurance)
- No Means of Payment (No Insurance)
- Other
- Unknown

n. Race (select all that apply):
- American Indian or Alaska Native
- Asian
- Black or African American
- Native Hawaiian or other Pacific Islander
- White
- Unknown

13.4 Registration Procedures

a. All site staff will use OPEN to enroll patients to this study. OPEN is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at https://open.ctsu.org, from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org, or from the OPEN Patient Registration link on the SWOG CRA Workbench.

b. Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes and the affirmation of eligibility on the Registration Worksheet has been signed by the registering investigator or another investigator designate. Site staff should refer to Section 5.0 to verify eligibility.

- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

c. The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

d. Further instructional information is provided on the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

13.5 Exceptions to SWOG registration policies will not be permitted.

a. Patients must meet all eligibility requirements.

b. Institutions must be identified as approved for registration.

c. Registrations may not be cancelled.

d. Late registrations (after initiation of treatment) will not be accepted.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data Submission Requirement

Data must be submitted according to the protocol requirements for **ALL** patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

14.2 Master Forms

Master forms can be found on the protocol abstract page on the SWOG website (www.swog.org) and (with the exception of the sample consent form and the Registration Worksheet) must be submitted on-line via the Web; see Section 14.3a for details.

14.3 Data Submission Procedures

a. Data collection for this study will be done exclusively through the Medidata Rave® clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, you must have an active CTEP-IAM account (check at https://ctepcore.nci.nih.gov/iam/) and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the LPO or participating organization roster at the enrolling site.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the “accept” link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members’ website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

b. You may also access Rave® via the SWOG CRA Workbench. Go to the SWOG web site (http://swog.org) and logon to the Members Area using your SWOG Roster ID Number and password. After you have logged on, click on *Workbenches*, then *CRA Workbench* to access the home page for the CRA Workbench and follow the link to Rave® provided in the left-hand navigation panel.

To access the CRA Workbench the following must be done (in order):

1. You are entered into the SWOG Roster and issued a SWOG Roster ID Number,
2. You are associated as an investigator or CRA/RN at the institution where the patient is being treated or followed,
3. Your Web User Administrator has added you as a web user and has given you the appropriate system permissions to view data for that institution.

For assistance with points 1 and 2 call the Operations Office at 210/614-8808. For point 3, contact your local Web User Administrator (refer to the "Who is my Web User Administrator?" function on the swog.org Members logon page).

For difficulties with the CRA Workbench, please email technicalquestion@crab.org.

c. Institutions participating through the Cancer Trials Support Unit (CTSU) please refer to the CTSU Participation Table.

14.4 Data Submission Overview and Timepoints

a. WITHIN 7 DAYS OF REGISTRATION:

S1607 Onstudy Form

S1607 Baseline Abnormalities Form

S1607 Baseline Tumor Assessment Form

Pathology report documenting histologic confirmation of melanoma*

Radiology reports from all scans performed to assess disease at baseline*

Physician report documenting any measurement of skin lesions made during a physical examination*

*NOTE: Upload reports via the Source Documentation: Baseline form in Rave®.

b. WITHIN 7 DAYS AFTER EACH CYCLE OF TREATMENT (1 cycle =21 days)

Submit the following:

S1607 Treatment Form

S1607 Adverse Event Form

c. WITHIN 14 DAYS AFTER EACH DISEASE ASSESSMENT (SEE STUDY CALENDAR FOR SCHEDULE):

Submit the following:

S1607 Follow-Up Tumor Assessment Form

Radiology reports from all scans performed to assess disease*.

Physician report documenting any measurements of skin lesions made during a physical examination.*

*NOTE: Upload reports via the Source Documentation: Follow-Up form in Rave®.

d. WITHIN 14 DAYS OF DISCONTINUATION OF TREATMENT:
Submit the following:

Off Treatment Notice

S1607 Treatment Form

S1607 Adverse Event Form

e. WITHIN 14 DAYS OF PROGRESSION/RELAPSE:

S1607 Follow-Up Tumor Assessment Form

Radiology reports from all scans performed to assess disease*. Physician must note tumor measurement in patient records.

Physician report documenting any measurements of skin lesions made during a physical examination.*

If patient is going to discontinue protocol treatment at the time of progression, also submit the materials specified in Section 14.4d.

See Section 15.0 for specimen submission requirements.

*NOTE: Upload reports via the Source Documentation: Follow-Up form in Rave®.

f. EVERY 6 MONTHS FOR THE FIRST YEAR AFTER REGISTRATION YEAR AND THEN ANNUALLY UNTIL 5 YEARS FROM REGISTRATION OR DEATH (whichever occurs first):

Submit the following:

Advanced Melanoma Follow Up Form

Late Effects Form (if prior to treatment for progression or relapse or a second primary, and prior to non-protocol treatment, the patient experiences any severe [Grade ≥ 3] long term toxicity that has not been previously reported)

g. WITHIN 4 WEEKS OF KNOWLEDGE OF DEATH:
Submit the following:

Notice of Death

Advanced Melanoma Follow Up Form, or if patient was on treatment at the time of death, the materials specified in Section 14.4d.

15.0 SPECIAL INSTRUCTIONS

15.1 Translational Medicine

Specimens for Translational Medicine (required for patient):

a. Specimens must be submitted at the time points listed below. Collection instructions are outlined in Section 15.1c and submission instructions are outlined in Section 15.1e.

b. Specimens must be submitted at the following times (see Section 9.0):

1. Tumor Samples

Archival Tissue (collected before the previous anti-PD-1 or anti-PD-L1 therapy): If available, please submit 30 unstained slides (or maximum amount that can be submitted per availability or institutional policy) x 4 um each***.

Fresh Biopsy: At least 2 passes/cores from 14-gauge coring needle, 3 passes/cores from 18-gauge coring needle, or equivalent volume via other techniques, from each biopsied lesion. While cores may be formalin fixed in the same container, each core should be embedded in a separate paraffin block. Tissue from each block should be submitted. If no block can be shipped, submit 30 unstained slides (or maximum amount that can be submitted per availability or institutional policy) x 4 um each, from each block. Tissue must be collected prior to Day 1 of protocol treatment* and again 28 calendar days (+/- 7 calendar days) after starting protocol treatment**.

	Baseline (mandatory)	Day 28 (mandatory)	Progression (optional)
Cohort A (with visceral lesions)			
• Injected skin/nodal lesion		x	Site of progression (the fastest growing lesion)
• Un-injected skin/nodal lesion	x		
• Visceral lesion		x	
Cohort B (no visceral lesions)			
• Injected skin/nodal lesion		x	Site of progression (the fastest growing lesion)
• Un-injected skin/nodal lesion	x	x	

* Biopsy on or prior to Day 1 should be performed prior to Day 1. If it is not feasible to prospectively obtain this biopsy, tissue collected at any

time since demonstrated progression on PD-1 or PD-L1 therapy may be substituted provided that 30 unstained slides are available.

** The tissue samples may be batch shipped after collection of tissue from Day 28 (+/- 7 calendar days) biopsy. Tissue blocks/slides should be stored at 4°C before shipping.

*** If archival tissue is not available for submission, proceed as usual per directed time points for biopsy collection. Archival tissue is required if available and patient consents.

With patient consent, remaining specimens will be banked for future use.

2. Blood Samples:

20 mL of peripheral blood for PBMCs collected in purple-top EDTA tube(s) at:

- Baseline (after registration but prior to starting treatment on Day 1 within 7 days prior to starting treatment per Section 13.1.)
- Week 2
- Week 4
- Week 10
- Progression

Whole blood must be sent via overnight courier (e.g. FedEx) within 24 hours of collection. Specimens may be shipped Monday through Thursday using only overnight delivery to arrive Monday through Friday. No blood should be collected or shipped on Friday or right before a holiday. Additionally, since blood must be logged and shipped the day of collection, blood should not be collected prior to subject registration.

With patient consent, remaining specimens will be banked for future use.

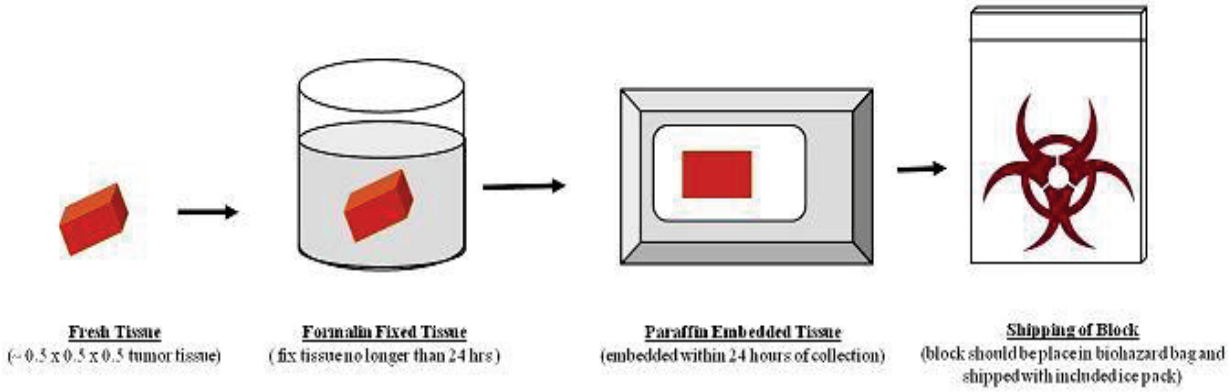
NOTE: If any blood collection timepoint was missed, sites must draw blood at the next patient visit for lab work.

c. Specimen Collection Instructions

1. Standard collection of Paraffin Embedded Tissue Block.
   - Place the fresh tissue in formalin. Do Not Exceed 24 hours fixation time.
   - Fixed tissue must be paraffin embedded within 24 hours.
   - Send H & E (Hematoxylin and Eosin) stained section if it is routine practice for the site. Otherwise, sending the block without the H&E slide is adequate.

2. Standard Instructions for Shipping Paraffin Embedded Tissues:
   - Include in shipment:
     i. Tissue as outlined above. Please indicate the location of the biopsied lesions (skin, lymph node, lung, liver, etc.)
     ii. A copy of the packing/shipping list produced by the SWOG Online Specimen Tracking System.
   - Ship paraffin embedded tissue according to the shipping guidelines for ambient specimens in the General Specimen Submission Instructions below.

NOTE: Paraffin tissue blocks will NOT be returned to the submitting institution unless it is required for patient care. If the block is needed for patient care, a written request must be submitted to the Study Chair with a rationale for the return.



3. Standard Instructions for Collecting and Shipping Fresh Whole Blood Specimens.
   - Use 10 ml vacutainer tubes with EDTA to collect whole blood.
     i. If your site does not have the recommended size of vacutainer tubes required by the treatment protocol, other sized tubes may be used to collect the required/requested amount of blood.
     ii. Avoid using < 3mL collection tubes.
     iii. Pre-label vacutainer tube(s) according to specimen labeling requirements indicated in the General Specimen Submission Instructions.
   - Use aseptic techniques and draw blood from the patient into the vacutainer tube(s). The amount of blood required will vary per protocol.
   - Immediately after the blood is drawn, thoroughly mix the blood with the anticoagulant by gently inverting the vacutainer tube(s) multiple times.
   - Store whole blood prior to shipping at room temperature. Do not freeze the whole blood. Storage time longer than 24 hours should be noted on the specimen shipping form.
   - Whole blood should be shipped the same day (day of collection) preferably using Federal Express, Priority Overnight service. Use of other courier services may delay package receipt.
     i. Specimens may be shipped Monday through Thursday using only overnight delivery to arrive Monday through Friday. No blood should be collected or shipped on Friday or right before a holiday.
     ii. During the months of April-September, ship fresh specimens on a cold pack. During the months of October-March, insulate fresh specimens to keep from freezing due to weather (ex. wrap specimen in bubble wrap).

For packaging instructions, refer to the shipping guidelines for ambient specimens in the General Specimen Submission Instructions outlined above.

d. Specimen collection kits are not being provided for this submission; sites will use institutional supplies.

e. SHIPPING SAMPLES

1. SWOG Specimen Tracking System (STS)
All specimen submissions for this study must be entered and tracked using the SWOG online Specimen Tracking system. SWOG members may log on the online system via the CRA Workbench. To access the CRA Workbench, go to the SWOG Web site (http://swog.org) and logon to the Members Area. After you have logged on using your SWOG roster ID number and password, click on the *CRA Workbench* link to access the home page for CRA Workbench website. Non- SWOG users may log into SpecTrack using their CTSU UserID and password on the SpecTrack login page located at https://crawb.crab.org/SpecTrack/Logon.aspx (select the option "SWOG – SWOG – CTSU"). SpecTrack start-up instructions (both written and demo) are available after signing in to SpecTrack.

A copy of the Shipment Packing List produced by the online Specimen Tracking system should be printed and placed in the pocket of the specimen bag if it has one, or in a separate resealable bag. The Specimen Submission Form is NOT required when the online system is used.

ALL SPECIMENS MUST BE LOGGED VIA THIS SYSTEM; THERE ARE NO EXCEPTIONS.

To report technical problems with Specimen Tracking, such as database errors or connectivity issues, please send an email to technicalquestion@crab.org. For procedural help with logging and shipping specimens, there is an introduction to the system on the Specimen Tracking main page (http://dnet.crab.org/SpecTrack/Documents/Instructions.pdf); or contact the Data Operations Center at 206/652-2267 to be routed to the Data Coordinator for further assistance.

In the online specimen tracking system, the appropriate SWOG laboratory for submission of tissue and blood samples for SWOG Repository Submission and testing is identified as follows:

Lab #224: The Ribas Laboratory
Attention: Agustin Vega-Crespo
Medical Receiving – Study **S1607**
CHS 54-200
650 CHARLES E YOUNG DR S
UCLA Medical Center
Los Angeles, CA 90095
Phone: 310-825-2676
Fax: 310-825-2493

Contacts:
Beata Berent-Maoz
E-mail: BBerent@mednet.ucla.edu
Agustin Vega-Crespo
Email: avegacrespo@mednet.ucla.edu

2. Federal guidelines for the shipment of blood products:
   a. The tube must be wrapped in an absorbent material.
   b. The tube must then be placed in an AIRTIGHT container (like a resealable bag).
   c. Pack the resealable bag and tube in a Styrofoam shipping container.
   d. Pack the Styrofoam shipping container in a cardboard box.
   e. Mark the box "Biohazard".

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent
The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review
This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Drug Accountability
An investigator is required to maintain adequate records of the disposition of investigational drugs according to procedures and requirements governing the use of investigational new drugs as described in the Code of Federal Regulations 21 CFR 312.

Publication and Industry Contact
The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between Merck and Amgen (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines in addition to the provisions in the "Intellectual Property Option to Collaborator"
(http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award apply to the use of the Agent in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations which would tend to restrict NCI's participation in the proposed combination protocol.

b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to the Collaborator(s) for Phase III studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to the Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/media presentation should be sent to:

   E-mail: ncicteppubbs@mail.nih.gov

   The Regulatory Affairs Branch will then distribute them to the Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of the Collaborator's confidential/proprietary information.

   This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis by FTP burst of data. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site

(http://ctep.cancer.gov/reporting/cdus.html).

Note: If your study has been assigned to CDUS-Complete reporting, **all** adverse events (both routine and expedited) that have occurred on the study and meet the mandatory CDUS reporting guidelines must be reported via the monitoring method identified above. If your study has been assigned to CDUS-Abbreviated reporting, no adverse event reporting (routine or expedited) is required to be reported via CDUS, but expedited adverse events are still required to be submitted via CTEP-AERS.

Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

Confidentiality
Please note that the information contained in this protocol is considered confidential and should not be used or shared beyond the purposes of completing protocol requirements until or unless additional permission is obtained.

Adverse Event Reporting Requirements

a. Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol.

b. Reporting method

This study requires that expedited adverse events be reported using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted to the SWOG Operations Office electronically via the CTEP-AERS Web-based application located at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm

c. When to report an event in an expedited manner

Some adverse events require 24-hour notification (refer to Table 16.1) via CTEP-AERS.

In the rare event when internet connectivity is disrupted a 24-hour notification is made to NCI by telephone at 301-897-7497. An electronic report MUST be submitted immediately upon re-establishment of internet connection.

When the adverse event requires expedited reporting, submit the report within the number of calendar days of learning of the event specified in Table 16.1.

Any supporting documentation should be submitted to CTEP per NCI guidelines for AE reporting located at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pd

d. Other recipients of adverse event reports

The SWOG Operations Office will forward reports and documentation to the appropriate regulatory agencies and drug companies as required.

Adverse events determined to be reportable to the Institutional Review Board responsible for oversight of the patient must be reported according to local policy and procedures.

e. Expedited reporting for investigational agents

Expedited reporting is required if the patient has received at least one dose of the investigational agent(s) as part of the trial. Reporting requirements are provided in Table 16.1. The investigational agents used in this study are pembrolizumab (MK-3475) and talimogene laherparepvec (T-VEC). If there is any question about the reportability of an adverse event or if on-line CTEP-AERS cannot be used, please telephone or email the SAE Specialist at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.1
Phase I and Early Phase II Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a CTEP IND within 30 Days of the Last Administration of the Investigational Agents/Intervention[1] pembrolizumab (MK-3475) and talimogene laherparepvec (T-VEC)

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

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

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR or Section 16.1f.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:
- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:
- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

May 5, 2011

f. Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase I and Early Phase II Studies Utilizing an Agent under a CTEP IND:

1. **Group-specific instructions**
Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements. In addition, you may be asked to submit supporting clinical data to the Operations Offices in order to complete the evaluation of the event. If requested, the supporting data should be sent within **5 calendar days** by fax to 210-614-0006. Supporting clinical data submitted should include:
    - Printed copy of the first page of the CTEP-AERS Report.
    - Copies of clinical sourced documentation of the event.
    - If applicable, and they have not yet been submitted to the SWOG Data Operations Center copies of Off Treatment Notice and/or Notice of Death.

g. Accidental talimogene laherparepvec (T-VEC) exposure and suspected infection in study patients receiving talimogene laherparepvec (T-VEC):

If the patient receiving talimogene laherparepvec (T-VEC) on study has developed signs or symptoms of herpetic infection, the event must be reported to Amgen AND CTEP-AERS and patient should be followed up by the study team for viral assays: Report to CTEP-AERS as SAE.
NOTE: Refer to Section 18.3 for Additional Reporting Requirements

h. Reporting Secondary Malignancy, including AML/ALL/MDS

1. A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND to be reported via CTEP-AERS. Three options are available to describe the event.

- Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic Leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

Second Malignancy: A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

For more information see:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf

2. Any supporting documentation should be submitted to CTEP per NCI guidelines for AE reporting located at http://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/aeguidelines.pdf

   A copy of the report and the following supporting documentation must also be submitted to SWOG Operations Office within 30 days by fax to 210-614-0006 or mail to the address below:

   - a copy of the pathology report confirming the AML/ALL /MDS diagnosis
   - (if available) a copy of the cytogenetics report

   SWOG
   ATTN: SAE Program
   4201 Medical Drive, Suite 250
   San Antonio, Texas 78229

   NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the report must be submitted for the most recent trial.

i. Reporting Pregnancy, Fetal Death, and Death Neonatal

1. **Pregnancy** Study participants who become pregnant while on study; that pregnancy should be reported in an expedited manner via CTEP-AERS as **Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)"** under the **Pregnancy, puerperium and perinatal conditions** SOC.

   Additionally, the pregnancy outcome for patients on study should be reported via CTEP-AERS at the time the outcome becomes known, accompanied by the same Pregnancy Report Form used for the initial report.

2. **Fetal Death** Fetal Death defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation" should be reported expeditiously as **Grade 4 "pregnancy, puerperium and perinatal conditions – Other (pregnancy loss)" under the Pregnancy, puerperium and perinatal conditions** SOC.

3. **Death Neonatal** Neonatal death, defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention should be reported expeditiously.

   A neonatal death should be reported expeditiously as **Grade 4 "General disorders and administration – Other (neonatal loss)"** under the **General disorders and administration** SOC.

*Fetal death and neonatal death should **NOT** be reported as a Grade 5 event. If reported as such, the CTEP-AERS interprets this as a death of the patient being treated.*

NOTE: When submitting CTEP-AERS reports for "Pregnancy, "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should also be completed and faxed with any additional medical information to 301-230-0159. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

The Pregnancy Information Form is available at:
http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm

j. Additional Reporting Requirements for T-VEC-associated adverse events and biosafety incidents.

Please see Appendix 18.3.

17.0 BIBLIOGRAPHY

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18.0 APPENDIX

18.1 Anti-PD-1 and Anti-PD-L1 Agents

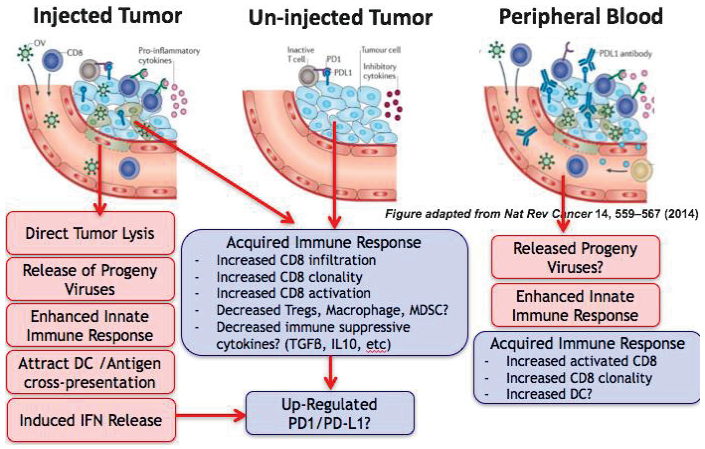
- Atezolizumab
- Avelulmab
- Durvalumab
- Nivolumab
- Pembrolizumab (MK-3475)

18.2 Translational Medicine Methods

1. **Data storage and computational infrastructure:** To optimally perform computational analysis on the large amount of genomic and imaging data to be generated from this study, it is expected that appropriate cloud computing infrastructure with the necessary analysis pipeline is required for the storage and computation of these data. One such computational infrastructure and resource available for this study is through the collaboration with the Parker Institute for Cancer Immunotherapy.

2. **Quantitative analysis of T-cell infiltration:** Given local virus replication and GM-CSF release, we anticipate increased CD8+ Tcell infiltration in the tumors after combination of intratumoral injection of talimogene laherparepvec (T-VEC) and PD-1 blockade starts. Slides taken from standard formalin-fixed paraffin-embedded (FFPE) tissue blocks obtained from baseline, Day 28 (on treatment), and upon progression to determine the presence of CD8+ T-cells inside tumors and in the invasive margin. Slides will be analyzed using quantitative digital pathology following the methods described. *(1)*

Figure 2: Proposed mechanism of action of T-VEC.



All slides will be scanned at an absolute magnification of X200 (resolution of 0.5 mm/pixel). An algorithm was designed based on pattern recognition that quantified immune cells within S100-positive areas (tumor) and S100-negative areas (invasive margin). Image analysis based on RGB (red, green, blue) spectra will be used to detect all cells by counterstaining with haemotoxylin (blue), and DAB or fast red. CD8 expression is determined using two read-outs that are independent of each other to account for tumor heterogeneity: cell density (number of positive cells /mm^2) and percentage cellularity (number of positive cells/number of nucleated cells) using Indica Labs Halo platform.

3. **Analysis of TCR clonality in tumors and in blood: To answer the question** whether the T-cell response is targeting specific tumor antigen (mono-clonal) or a non-specific process (poly-clonal) in both the tumors and in the peripheral blood, we will analyze TCR clonality by deep sequencing the TCR Vβ CDR region using the ImmunoSeq assay from Adaptive Biotech as described. *(2)* PBMC from blood and thick slides from FFPE tissues taken at baseline and Day 28 after initiation of treatments, will be used to isolate DNA for TCR Vβ sequencing. This analysis will provide information about the clonality or diversity of T-cells infiltrating tumors and circulating in the blood. DNA analysis will be performed by the UCLA Immunogenetics core laboratory (CLIA approved lab).

DNA will be isolated from FFPE thick cuts or PBMC followed by extraction using a DNeasy kit (Qiagen). Melanin will be removed from visibly pigmented melanoma samples using a PCR Inhibitor Removal kit (ZymoResearch). TCR Vβ CDR3 regions will be amplified and sequenced using the survey ImmunoSeq assay in a multiplexed PCR method using 45 forward primers specific to TCR Vβ gene segments and 13 reverse primers specific to TCR Vβ gene segments (Adaptive Biotechnologies). Reads of length 87bp will be obtained using the Illumina HiSeq System. For each sample, Shannon entropy will be calculated on the clonal abundance of all productive TCR sequences in the data set. Shannon entropy will be normalized to the range by dividing Shannon entropy by the logarithm of the number of unique productive TCR sequences in the data set. This normalized entropy value will be then inverted (normalized entropy) to produce our clonality metric.

4. **Analysis of tumor immune microenvironment**: Local viral replication and antigen presentation, as well as GM-CSF release, will attract dendritic cell infiltration, and change the global tumor immune microenvironment in favor of activating the immune system to target the tumor. In addition, interferon produced by inflammatory cells in an attempt to eradicate the viral infection, can up-regulate PD-L1 expression, providing rationale for synergy of talimogene laherparepvec (T-VEC) with PD-1 blockade.

   Slides taken from standard FFPE tissue blocks obtained from baseline, the on-treatment biopsy (Day 28) and upon progression will be stained by IHC for PD-L1 (SP142, Spring Bioscience), PD-1, dendritic cell markers (CD80, CD86), immune suppressive cell markers (anti-FoxP3 for Treg, anti-CD68 antibody for macrophage, clone PG-M1, DAKO, anti-CD14 for monocyte, CD15 for granulocytes), or other immune related functional expression and biomarkers. Slides will be analyzed using quantitative multiplexed digital pathology. *(3, 4)*

   Immunostaining of the rest of the targets will be performed at the UCLA Anatomic Pathology IHC Laboratory (CLIA approved lab) on Leica Bond III autostainers using Leica Bond ancillary reagents and REFINE polymer DAB detection system. All stained slides will be evaluated in a blinded fashion by one dermatopathologist and one investigator trained to identify the features of melanoma, and the presence of positive stained targets within the tumor parenchyma (tumor) and the connective tissue surrounding the tumor (invasive margin).

   Analysis of mRNA expression by Nanostring allowed demonstrating that an interferon gamma signature is predictive of response with pembrolizumab *(5)*, which is logical as it is an indirect measure of a pre-existing infiltrate by T cell with specificity to tumor antigens leading to the production of interferon gamma and the adaptive expression of PD-L1. Further analyses of mRNA expression demonstrated a dominant set of genes in patients whose tumors did not respond to anti-PD-1, which we termed innate PD-1 resistance signature (IPRES). *(6)* We will consider to extract total RNA from FFPE samples and do nanostring analysis for global evaluation of immune activation. With these studies we anticipate to obtain a comprehensive view of the effects of the combined therapy of T-VEC and pembrolizumab to reverse resistance to single agent anti-PD-1 therapy.

5. **Analysis of mutational load by whole exome sequencing:**
   It is currently unknown which antigens are being recognized by T-cells attacking tumors after release of PD-1 blockade. But evidence from studies with other immunotherapies suggests that most of these antigens are neoepitopes resultant from somatic mutations. In a recent experience, whole exome sequencing was performed on tumors and matching blood of patients treated with CTLA4 blockade

with ipilimumab or tremelimumab. *(7)* Neoantigen peptides were tested for the ability to activate lymphocytes from ipilimumab-treated patients. Mutational load was associated with clinical benefit (p=0.01), but alone was not sufficient to predict benefit. Using genome-wide somatic neoepitope analysis and patient-specific HLA typing, the authors identified candidate tumor neoantigens for each patient. Recently, a correlation of tumor mutational load and response to PD-1 antibody therapy was also reported in NSCLC patients treated with pembrolizumab (MK-3475). *(8)* We want to evaluate whether tumor mutational load and circulating tumor DNA (ctDNA) profile are associated with response to talimogene laherparepvec (T-VEC) + pembrolizumab (MK-3475) combination in this anti-PD1 refractory melanoma population. In addition, since the IFN pathway is critically important for the efficacy of the talimogene laherparepvec (T-VEC) oncolytic viral therapy, we want to evaluate mutations in the IFN signaling pathway and the correlation with tumor specific immune response of the talimogene laherparepvec (T-VEC) + pembrolizumab (MK-3475) combination therapy.

DNA will be isolated from thick slides of FFPE tissues and *PBMC via commercial kit (i.e. Qiagen AllPrep DNA/RNA FFPE kit, cat 80234). Whole exome sequencing (WES), including probe-based exon capture, library preparation, and high throughput 100bp paired-end sequencing on the Illumina HiSeq2500 platform will be performed at the UCLA Immunogenetics core laboratory. DNA from the same patient's PBMC (preferably) or other non-cancerous tissue will be isolated and sequenced for baseline comparison and differentiation of germline SNPs from true somatic mutations. Read mapping and data preprocessing will be performed according to the Broad Institute Best Practices Guidelines for the Genome Analysis Toolkit (version 3), and mutation detection will require a consensus call among several published programs (Varscan2, MuTect, GATK HaplotypeCaller). Mutational load will be quantified as the number of nonsynonymous somatic mutations per MB. Circulating tumor DNA profiling from patient-matched baseline and on-treatment plasma samples will be performed to determine the amount or fraction of ctDNA corresponding to the genetic profile of the patient tumor biopsies. Taken together, this will evaluate whether tumor mutational load and circulating tumor DNA (ctDNA) profile are associated with response to talimogene laherparepvec (T-VEC) + pembrolizumab (MK-3475) combination in this anti-PD1 refractory melanoma population.

Translational Medicine Objectives

a. For all analyses, if the distributions are far from normal or subject to influential points, then we will use robust, rank based or non-parametric approaches such as the Wilcoxon test. Similarly, we will conduct adjusted analyses to accommodate any potential confounders that may arise, e.g. technical batch.

   To assess whether there is a change in T-cell infiltration from baseline to Day 28, we compare CD8 expression levels between baseline and week 2 using a paired t-test. We will control type I error at the two-sided alpha=0.05 level. For Cohort A, with 17 eligible patients, we anticipate 80% power to detect a change in mean CD8 expression from baseline to Day 28 of 0.72 standard deviations. Among patients that progress, we will repeat the analysis to compare CD8 expression at progression to baseline with the understanding that there is potentially informative missingness in that patients who do not progress may have higher infiltration.

   We will further assess whether increased T-cell infiltration from baseline to Day 28 is associated with higher ORR. Specifically, we will compute the change in CD8 expression between Day 28 and baseline and compare the change in CD8 expression between objective responders and non-

objective responders using a two-sample t-test at the two-sided 0.05 level. For Cohort A, with 17 eligible patients and assuming 25% of patients have a response, we anticipate 80% power to detect a difference in mean change in CD8 expression of 1.68 standard deviations. Subsequently, to assess the hypothesis that TCR clonality is higher in patients who respond to the combination therapy, suggesting that the T-cells are targeting the tumor, we will compute the clonality metric as the normalized Shannon entropy for all patients at baseline and Day 28. We will then compute the change in clonality metric from baseline to Day 28. The change in clonality will be compared between responders and non-responders using a two-sample t-test with significance determined at the two-sided alpha=0.05 level. For Cohort A, assuming that 25% of patients respond, then we anticipate 80% power to detect a difference in clonality change of 1.68 standard deviations. We will repeat the analyses examining TCR clonality in peripheral blood. Finally, we will assess whether ctDNA fraction at baseline and Day 28 is associated with ORR using a two-sample t-test at the two-sided 0.05 level. For Cohort A, with 17 eligible patients and assuming 25% of patients have a response, we anticipate 80% power to detect a difference in mean ctDNA fraction of 1.68 standard deviations.

To assess whether the tumor microenvironment is improved by injection with talimogene laherparepvec (T-VEC), we will examine the expression of approximately 10 candidate immune markers: PD-L1, PD-1, dendritic cell markers (CD80, CD86), immune suppressive cell markers (anti-FoxP3 for Treg, anti-CD68 antibody for macrophage, clone PG-M1, DAKO, anti-CD14 for monocyte, and CD15 for granulocytes). For each marker, we will test for a difference in expression between baseline and the Day 28using paired t-tests at the alpha = 0.005 level to accommodate multiple comparisons. We will subsequently test the association between change in expression level of each marker (from baseline to Day 28) with response using a two-sample t-test at the alpha = 0.005 level. For Cohort A, in comparing expression at baseline to Day 28, with 17 eligible patients, we anticipate 80% power to detect a change in mean expression of 1.0 standard deviations. In comparing change in expression between responders and non- responders, assuming 25% of patients respond durably, then we anticipate 80% power to detect a difference in mean change in expression of 2.3 standard deviations.

To assess the hypothesis that higher mutational load at baseline or at Day 28 is associated with durable response rate, we will assess the association between overall mutational load at each time point, separately, and durable response rate. Specifically, we will use logistic regression to regress response status on the mutation rates (at baseline or at Day 28) and use a 1-df test to obtain a p-value for the association between durable response and mutation rate. We will control the type I error at the two-sided alpha=0.10 level. If logistic regression behaves poorly, e.g. due to low response rates, we will consider using robust or flexible alternatives.

b. For all analyses, if the distributions are far from normal or subject to influential points, then we will use robust, rank based or non-parametric approaches such as the Wilcoxon test. Similarly, we will conduct adjusted analyses to accommodate any potential confounders that may arise, e.g. technical batch.

To assess whether there is a change in T-cell infiltration from baseline to Day 28, we compare CD8 expression levels between baseline and Day 28 using a paired t-test. We will control type I error at the two-sided alpha=0.05 level. For Cohort B, with 25 eligible patients, we anticipate 80% power to detect a change in mean CD8 expression from baseline to Day 28 of 0.58 standard deviations. Among patients that progress, we will repeat the analysis to compare CD8 expression at progression to baseline with the understanding that there is potentially informative missingness in that patients who do not progress may have higher infiltration.

We will further assess whether increased T-cell infiltration from baseline to Day 28 is associated with higher ORR. Specifically, we will compute the change in CD8 expression between Day 28 and baseline and compare the change in CD8 expression between responders and non-responders using a two-sample t-test at the two-sided 0.05 level. For Cohort B, with 25 eligible patients and assuming 30% of patients have a response, we anticipate 80% power to detect a difference in mean change in CD8 expression of 1.28 standard deviations.

We will first assess whether TCR clonality within the tumor increases following treatment with combination therapy. Specifically, we will test for difference in mean normalized Shannon entropy for all patients between baseline and Day 28. For Cohort B, with 25 eligible patients, we anticipate 80% power to detect a change in mean normalized Shannon entropy from baseline to Day 28 of 0.58 standard deviations. We will repeat the analysis to compare TCR clonality at progression to baseline among patients who progress. Subsequently, to assess the hypothesis that TCR clonality is higher in patients who respond to the combination therapy, suggesting that the T-cells are targeting the tumor, we will compute the clonality metric as the normalized Shannon entropy for all patients at baseline and Day 28. We will then compute the change in clonality metric from baseline to Day 28. The change in clonality will be compared between responders and non- responders using a two-sample t-test with significance determined at the two-sided alpha=0.05 level. For Cohort B, assuming that 30% of patients respond, then we anticipate 80% power to detect a difference in clonality change of 1.28 standard deviations. We will repeat the analyses examining TCR clonality in peripheral blood. Finally, we will assess whether ctDNA fraction at baseline and Day 28 is associated with ORR using a two-sample t-test at the two-sided 0.05 level. For Cohort B, with 25 eligible patients and assuming 30% of patients have a response, we anticipate 80% power to detect a difference in mean ctDNA fraction of 1.28 standard deviations.

To assess whether the tumor microenvironment is improved by injection with talimogene laherparepvec (T-VEC), we will examine the expression of approximately 10 candidate immune markers: PD-L1, PD-1, dendritic cell markers (CD80, CD86), immune suppressive cell markers (anti-FoxP3 for Treg, anti-CD68 antibody for macrophage, clone PG-M1, DAKO, anti-CD14 for monocyte, and CD15 for granulocytes). For each marker, we will test for a difference in expression between baseline and the Day 28 using paired t-tests at the alpha = 0.005 level to accommodate multiple comparisons. We will subsequently test the association between change in expression level of each marker (from baseline to Day 28) with response using a two-sample t-test at the alpha = 0.005 level. For Cohort B, in

comparing expression at baseline to Day 28, with 25 eligible patients, we anticipate 80% power to detect a change in mean expression of 0.80 standard deviations. In comparing change in expression between responders and non-responders, assuming 30% of patients respond, then we anticipate 80% power to detect a difference in mean change in expression of 1.73 standard deviations.

To assess the hypothesis that higher mutational load at baseline or at Day 28 is associated with response rate, we will assess the association between overall mutational load at each time point, separately, and response rate. Specifically, we will use logistic regression to regress response status on the mutation rates (at baseline or at Day 28) and use a 1-df test to obtain a p-value for the association between response and mutation rate. We will control the type I error at the two-sided alpha=0.10 level. If logistic regression behaves poorly, e.g. due to low response rates, we will consider using robust or flexible alternatives.

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18.3 Site Requirements Based on Guidelines from the NIH Office of Scientific Policy (OSP) (Adapted for CTEP-sponsored T-VEC Protocols)

Because talimogene laherparepvec (T-VEC) is a gene transfer agent, all protocols should follow the NIH Office of Scientific Policy (OSP) guidelines, including protocol submission, AE reporting and Annual Reports to OSP. Compliance with the OSP requirements is the responsibility of the Principle and Participating. Investigators should review the OSP website (http://osp.od.nih.gov/sites/default/files/resources/NIH_Guidelines_PRN_1-sided.pdf) for complete instructions. In addition, all participating sites should follow the guidelines of local Institutional Biosafety Committee (IBC).
Key (but not all) OSP requirements are outlined below:

1) **Registration of protocol with OSP**: (Appendix M-I-A and M-I-B of the OSP guidelines https://osp.od.nih.gov/wp-content/uploads/NIH_Guidelines.html#_Toc446948494

The Principle Investigator or coordinating site IBC should submit the following to OSP via email at HGTprotocols@mail.nih.gov no less than 10 days before the anticipated protocol activation. (CTEP Protocol Information Office, pio@ctep.nci.nih.gov should be copied on this submission)

- The proposed protocol and Inform Consent Form (these documents do not have to be the final, IRB-approved version)
- Institutional Biosafety Committee (IBC)'s review or letter

Additional contact information is also available on the OSP website http://www.osp.od.nih.gov/about/contact-us/

An NIH OSP acknowledgement that the protocol registration process is complete will occur within the 10 working days prior to the anticipated date of enrollment. Final IBC approval may then be granted

2) **Reporting of Initiation of the Clinical Investigation (Appendix M-I-C-1 Packet of OSP** guidelines https://osp.od.nih.gov/wp-content/uploads/NIH_Guidelines.html#_Toc446948494):

The Principle Investigator of the protocol should submit the following documents to NIH OSP, no later than 30 working days after the first patient enrollment to the trial. (CTEP Protocol Information Office, pio@ctep.nci.nih.gov should be copied on this submission)

- A cover letter with the following information:
  - applicable NIH grant number(s)
  - the FDA IND number
  - any modifications to the protocol as required by FDA
  - the date of the initiation of the trial.
- A copy of the protocol approved by the local Institutional Biosafety Committee (IBC) and IRB;
- A copy of the informed consent document (ICD) approved by the Institutional Review Board (IRB);
- A copy of the final IBC approval from the clinical trial site,
- A copy of the final IRB approval;

3) **Requirement for all Participating Institutions** (Appendix M-I-C-2 Packet of OSP guidelines https://osp.od.nih.gov/wp-content/uploads/NIH_Guidelines.html#_Toc446948494) (CTEP Information Office, Protocol pio@ctep.nci.nih.gov should be copied on this submission)

- For patient enrollment, all participating sites should obtain approval from the local IBC before patients can be enrolled at the site. Local IBC guidelines such as safety reporting requirements should also be followed.
- The following should be submitted to OSP within 30 days of the first patient enrollment at the site:
  - IBC approval from the participating site;
  - IRB approval (if CIRB is used, submit CIRB approval);
  - IRB-approved informed consent document (ICD);
  - NIH grant number(s) if applicable.

4) **Annual Reports** (Appendix M-I-C-3 Annual Report https://osp.od.nih.gov/wp-content/uploads/NIH_Guidelines.html#_Toc446948494– by Principle Investigator or delegate

Within 60 days after the one-year anniversary of the date on which the investigational new drug (IND) application went into effect, and after each subsequent anniversary until the trial is completed, CTEP as the sponsor will submit the Annual Reports (for all T-VEC trials under the CTEP IND) containing information set forth in (a), (b), and (c) (see Appendix M-I-C-3 in the link above), which shall include Clinical Trial Information, Progress Reports and Analysis, and Updated Protocol.

5) **Reporting of SAEs**

CTEP as the sponsor will submit SAEs that are serious, unexpected and related (i.e. IND Safety Reports) to OSP at the same timeline as for FDA reporting.
SAEs or other AEs should be reported to local IBC per local IBC guidelines.

6) Site Registration (see section 13.2 for more information)

Special requirements for T-VEC protocols:

- *For patient enrollment for protocol initiation:* The Principle Investigator should submit Approval from the local IBC of the initial site (PI's or the coordinating site)
- *For patient enrollment at additional participating sites*: Local Institutional Biosafety Committee (IBC) approval is required before a site can enroll patients to T-VEC protocols.

18.4 Additional Reporting Requirements for talimogene laherparepvec (T-VEC) associated adverse events, biosafety incidents, and accidental exposure of Health Care Providers (HCPs) to talimogene laherparepvec (T-VEC)

a. Talimogene laherparepvec (T-VEC) Specific Reporting Guidelines for Amgen

Reporting is required for: (1) suspected herpetic events in treated patients; (2) suspected herpetic events in at-risk HCPs with direct or indirect exposure to talimogene laherparepvec (T-VEC); and 3) suspected herpetic events in the treated patient's close contacts. The mechanism, timing, and follow-up procedures are summarized in the table below and described below, in bullet (b) (for treated patients) and (c) (HCPs and close contacts).

Accidental Exposure and Herpetic Event Reporting Requirement Summary

Exposed Person	Reporter	Timeframe for Reporting to Amgen	Report Mechanism	Timing of Swab Collection	qPCR Testing Required ?	Responsible Party for Lesion Swabbing	qPCR Test Result Distribution*
Treated Patients with suspected herpetic lesions	Investigator	Within 24 hours of Investigator awareness	Contact **Amgen** at 1-855-IMLYGIC (1-855-465-9442) **AND** Report to **CTEP** through **CTEP-AERS See Section 16.1**	Collect swabs from suspected lesions within 3 days of appearance of symptoms	Yes, if consent obtained	Investigator	Sponsor, Investigator, and Amgen
HCP directly exposed to product (e.g., needle stick, splash back) **without** signs or symptoms of herpetic illness	HCP's Personal Physician or impacted person	Within 24 hours of Reporter awareness	Contact **Amgen** at 1-855-IMLYGIC (1-855-465-9442) to report event	N/A	N/A	N/A	N/A
HCP directly or indirectly exposed to product **with suspected herpetic lesions**	HCP's Personal Physician or impacted person	**Within 24 hours** of Reporter awareness	Contact **Amgen** at 1-855-IMLYGIC (1-855-465-9442) to report event	Collect swabs from suspected lesions within 3 days of appearance of symptoms	Yes, if consent obtained	HCP or HCP's Personal Physician	HCP's Personal Physician and Amgen
Close Contact (e.g., caregiver, spouse, child) **with suspected herpetic lesions**	Close Contact's Personal Physician or Close Contact	**Within 24 hours** of Reporter awareness	Contact **Amgen** at 1-855-IMLYGIC (1-855-465-9442) to report event	Collect swabs from suspected lesions within 3 days of appearance of symptoms	Yes, if consent obtained	Close Contact's Personal Physician	Close Contact's Personal Physician and Amgen

b. Accidental talimogene laherparepvec (T-VEC) exposure and suspected infection in study patients receiving talimogene laherparepvec (T-VEC):

If the patient receiving talimogene laherparepvec (T-VEC) on study has developed signs or symptoms of herpetic infection, the event must be reported to Amgen AND CTEP-AERS (See Section 16.1) and patient should be followed up by the study team for viral assays:

Notify Amgen immediately (within 24 hours) upon knowledge of suspected infection). Contact the Amgen Call Center at 1-855-IMLYGIC (1-855-465-9442).

- Patient should be seen by the study physician. The herpetic lesions should be tested for DNA specific to talimogene laherparepvec (T-VEC). This testing must occur within three days of the appearance of the symptoms:
- Swabs of cold sore, vesicles or any other lesions suspected to be herpetic in origin should be obtained.
- Amgen will provide the qPCR test manual for sample collection and shipment to Viracor
- qPCR or other testing for wild type HSV-1 is not required. A commercially available test should be ordered if the investigator believes it is clinically indicated.

c. Accidental Exposure of Health Care Provider (HCP) to talimogene laherparepvec (T-VEC) without herpetic symptoms and signs:

If the HCP is suspected to have been exposed to talimogene laherparepvec (T-VEC) (direct exposure, e.g. needle sticks, splash) without signs or symptoms of herpetic infection, the event must be reported to Amgen.

1. Report to Amgen by calling Amgen Call Center at 1-855-IMLYGIC (1-855-465-9442).

d. Accidental Exposure and Secondary Transmission of talimogene laherparepvec (T-VEC) to Close Contacts or Health Care Provider (HCP) with symptoms/signs of herpetic infection:

If a close contact or HCP is suspected to have been exposed to talimogene laherparepvec (T-VEC) (with signs or symptoms of herpetic infection, the event must be reported to Amgen. Amgen will provide instructions regarding follow up with physicians and talimogene laherparepvec (T-VEC) testing.

1. Report to Amgen immediately (within 24 hours) as symptoms or signs are observed. Contact the Amgen Call Center at 1-855-IMLYGIC (1-855-465-9442).

    - Amgen will provide close contacts/HPC with instructions to see physicians for management and evaluation of talimogene laherparepvec (T-VEC) DNA. This testing must occur within three days of the appearance of the symptoms.

    - The physicians of HCP or Close Contacts will be responsible for obtaining the swab of herpetic lesions and submitting it to talimogene laherparepvec (T-VEC) testing, per instructions from Amgen.

2. Also refer to instructions in the Information Sheet for Close Contacts.

    *NOTE: Close contacts in regions where talimogene laherparepvec (T-

VEC) is commercially available should contact their HCP to evaluate the lesions. In the US, suspected herpetic lesions should be reported to Amgen as instructed above. Close contacts have the option of follow-up testing for further characterization of the infection. This test is likely to be more reliable if it can be performed within the first three days of symptoms appearing.

*NOTE: Close contacts in regions where talimogene laherparepvec (T-VEC) is not commercially available (e.g. Canada) may contact their HCP for evaluation and appropriate treatment. They should come to the study site for sample collections for qPCR testing for suspected herpetic lesions. This test is likely to be more reliable if it can be performed in the first three days of symptoms appearing.

e. NIH Office of Science Policy (OSP) Reporting of Human Gene Transfer (talimogene laherparepvec (T-VEC)) Adverse Events (known or suspected), Associated Adverse Events and BioSafety Incidents

1. Any serious adverse event that is both unexpected and associated with the use of T-VEC (ie, there is a reasonable possibility that the event may have been caused by the use of T-VEC) must be clearly labeled as a Safety Report and reported to SWOG by fax to 210-614-0006 and the Institutional Biosafety Committee (IBC) (via local institutional procedures) within **7 days of site knowledge of the event**, using the form below (in addition to CTEP-AERS serious adverse event reporting. See Section 16.1).

PROTOCOL AND EVENT TYPE	
NIH/OBA (RAC) Protocol Number	**S1607**
FDA IND number	
Date this report completed:	
Seriousness of the AE (choose one)	Death Life-threatening Initial or prolonged hospitalization Disability Congenital anomaly Required intervention to prevent permanent impairment/damage Other medically important condition Non-serious
Severity of Event	Minimal Moderate Severe Life- Threatening Fatal
Was this event expected in terms of its severity?	Yes No
Was this event expected in terms of its specificity?	Yes No
Relationship of Event to gene transfer product	Unrelated Unlikely Possible Probable

PROTOCOL AND EVENT TYPE	
NIH/OBA (RAC) Protocol Number	**S1607**
	Definite
Attribution of AE Attribution of AE, continued	Concomitant medication Product Intervention Underlying disease Route of administration Other suspected cause (describe) _____
Type of report	Initial Follow-up
DEMOGRAPHICS	
PI Name	
Name of Clinical Trial Site/Organization	
PI Telephone Number	
PI E-mail Address	
Reporter name	
Reporter Telephone number	
Reporter E-mail address	
Research Participant's study identification number	
Research Participant's gender	
Research Participant's date of birth	
Research Participant's date of death	
Research Participant's weight in kgs	
Research Participant's height in cms	
Which Arm/Cohort/treatment group was the patient assigned to?	
Was patient dosed?	Yes No Information Not Available
What study agent was received:	IND agent Placebo Blinded Study Agent
Were there any Protocol Deviations/Violations/Exceptions for this participant?	Yes:_____ No

DETAILED ADVERSE EVENT INFORMATION	
ADVERSE EVENT DATE	
Description of Event	
Relevant tests (e.g. x-rays) and results	
Treatment (s) of Adverse Event (Include medications used to treat this event.)	
Name of Concomitant Medications (Do not include medications used to treat this event.)	
Pre-existing conditions/ relevant clinical history (if this is an oncology trial, please designate primary disease, e.g. ovarian cancer)	
Date(s) of treatment(s) of the adverse event	
Outcome of the event	Recovered/resolved Recovering/resolving Not recovered/not resolved Recovered/resolved with sequelae Fatal Unknown
Documentation accompanying the report (e.g., H& P, Progress Notes, Discharge Summary, Lab Reports, Other, etc.)	
Description of any “other” documentation	

PRODUCT AND DOSING INFORMATION	
Name of gene transfer product	
Vector type (e.g. adenovirus)	
Vector sub-type (e.g. type 5, also include relevant deletions)	
Lot number	
Was the agent manufactured at an NGVL?	
Route of administration	
Site of administration	
Did patient receive the dose specified in the protocol?	
If not, what dose was given?	
Date of first exposure to study agent?	
Date of most recent exposure to study agent?	
Total dose received prior to this event?	
Total dose quantity administered to patient to date	
Unit of measure for a single dose	
Dose quantity in a single administration	
If courses used, how many were given prior to this event?	
How many doses on the last course were given?	
Was the administration of this product stopped because of this adverse event?	
Name of other treatment (s) (medications, radiation, surgery) received by research participant as required by the protocol	

2. Any significant problems, violations of the NIH Guidelines, or any significant research-related accidents and illnesses must be reported to SWOG by fax to 210-614-0006 and the Institutional Biosafety Committee (IBC) (via local institutional procedures) within 7 days of site knowledge of the event along with the requested narrative below. Reports to SWOG must be submitted on the Form below by fax to 210-614-0006. This includes any spill, skin puncture, or accident involving T-VEC. Spills or accidents, resulting in an overt exposure must be **immediately reported to the NIH Office of Biotechnology Activities at: HGTprotocols@mail.nih.gov, SWOG and the Institutional IBC, at the contact information below**.

Does this incident involve research patient to the *NIH Guidelines*?	☐YES ☐NO If no, this incident does not require reporting to OSP
Institution Name:	
Date of Report:	
Reporter name and position:	
Telephone number:	
Email address:	
Reporter mailing address:	
Date of incident:	
Name of Principal Investigator:	
Is this an NIH-funded project?	☐YES ☐NO If yes, please provide the following information (if known) *NIH grant of contract number:* *NIH funding institute or center:* *NIH program officer (name, email address):*

What was the nature of the incident?	☐Failure to follow approved containment conditions ☐Failure to obtain IBC approval ☐Incomplete inactivation ☐Loss of containment ☐Loss of a transgenic animal ☐Personnel exposure ☐Spill ☐Other (please describe):
Did the Institutional Biosafety Committee (IBC) approve this research?	☐YES ☐NO If yes, date of approval:
What was the approved biosafety level of the research?	☐BL1 ☐BL2 ☐BL2+ ☐BL3 ☐BL3+ ☐BL4
What section(s) of the *NIH Guidelines* is the research subject to?	
Has a report of this incident been made to other agencies? If so, please indicate	☐CDC ☐Funding agency/sponsor ☐USDA ☐State or local Public Health ☐FDA ☐Law enforcement ☐EPA ☐Other (please describe): ☐OSHA
Nature of recombinant or synthetic material involved in incident (strain, attenuation, etc.)	

Please provide a narrative of the incident including a timeline of events. The incident should be described in sufficient detail to allow for an understanding of the nature and consequences of the incident. **Include the following information as applicable.**

A description of:

- The incident/violation location (e.g. laboratory biosafety level, vivarium, non-laboratory space)
- Who was involved in the incident/violation, including others present at the incident location?

  Note – please do not identify individuals by name. Provide only gender and position titles (e.g., graduate student, post doc, animal care worker, facility maintenance worker)
- Actions taken immediately following the incident/violation, and by whom, to limit any health or environmental consequences of the event
- The training received by the individual(s) involved and the date(s) the training was conducted
- The institutional or laboratory standard operating procedures (SOPs) for the research and whether there was any deviation from these SOPS at the time of the incident/violation
- Any deviation from the IBC approved containment level or other IBC approval conditions at the time of the incident/violation
- The personal protective equipment in use at the time of the incident/violation
- The occupational health requirements for laboratory personnel involved in the research
- Any medical surveillance provided or recommended after the incident
- Any injury or illness associated with the incident
- Equipment failures

DESCRIPTION OF INCIDENT: (use additional space as necessary)

Has the IBC reviewed this incident?	☐YES ☐NO
Please describe the root cause of this incident:	

Describe measures taken by the institution to mitigate any problems identified. For measures identified but not yet taken, please include a timeline for their implementation (use additional space as necessary):

- **Additional information may be requested by NIH OSP after review of this report depending on the nature of the incident.**

- **Submitting this completed template to NIH OSP does NOT fulfill the reporting requirements of other agencies. You should verify with the other parties to whom you must report whether the use of this template is acceptable.**

18.5 Information Sheet for Caregivers, Family Members, and Other Close Contacts to Clinical Trial Participants Being Given talimogene laherparepvec (T-VEC) and for Non-Study Health Care Providers (HCP)

Study Title: _____

NCI protocol #:_____ **Amgen Tracking #:_____**

The patient _____ is enrolled on the clinical trial above using the experimental drug **Talimogene laherparepvec (talimogene laherparepvec (T-VEC))**. This clinical trial is sponsored by the National Cancer Institute.

The PI Name: _____ and PI contact # _____

_____

Dear Family Members, Caregivers, other Close Contacts and non-study Healthcare Providers:

This Information Sheet is being provided to patients who has been enrolled in a clinical trial of Talimogene Laherparepvec (T-VEC**),** and their close contacts and Healthcare Providers not involved in the trial**.** A close contact is considered a person that lives with the Patient (household member), care-giver, sex partner, or shares a bed with the Patient or conducts other activities that could involve exchange of bodily fluids through close physical contact. Non-study HCP are HCPs not involved in the talimogene laherparepvec (T-VEC) clinical trials but are seeing patients receiving talimogene laherparepvec (T-VEC) or their close contacts.

The purpose of this Sheet is to inform you of 1) ***Potential risk of exposure to talimogene laherparepvec (T-VEC)***, 2) ***Precautions*** and 3) ***Instructions in the case of talimogene laherparepvec (T-VEC) transmission***. In the end of this document, Additional information about talimogene laherparepvec (T-VEC) for Healthcare Providers who are not involved in this trial

I. What is the Study Drug, Talimogene Laherparepvec (T-VEC)?

Talimogene laherparepvec (T-VEC) is an investigational drug that is being studied for the treatment of certain types of cancer. Talimogene laherparepvec (T-VEC) contains a weakened form of the Herpes Simplex Virus Type 1 (the “cold sore” virus or “HSV-1”).

II. Can talimogene laherparepvec (T-VEC) be spread to family members or other close contacts?

Talimogene laherparepvec (T-VEC) could potentially be spread to family or people who have close physical or intimate contact with the Patient after tumor(s) are injected with the study drug. So far there have been no reported cases in clinical trial participants who have received talimogene laherparepvec (T-VEC) of spreading talimogene laherparepvec (T-VEC) to family members or other close contacts. In clinical trials so far, no talimogene laherparepvec (T-VEC) has been detected outside of the dressing that is placed on top of the site where it was injected.

The naturally occurring herpes simplex virus is not transmitted through the air or water droplets (such as when coughing or sneezing). Spreading occurs through direct contact from one person to another, particularly if a cold sore or genital sore is present (for example, through kissing or having sexual intercourse or other

intimate contact). It may also be spread by sharing a razor, towel, dish that has come in contact with a sore or bodily fluids.

Spreading (transmission) of talimogene laherparepvec (T-VEC) may be similar to spreading of the naturally occurring herpes simplex virus, and spreading may be more likely if you have a break in your skin or a mucous membrane comes into contact with an injection site or body fluids of a treated patient. Unlike the naturally occurring virus, however, talimogene laherparepvec (T-VEC) is administered into tumor lesions and is not expected to be able to replicate effectively in other noncancerous tissues. There have been no cases of spreading of talimogene laherparepvec (T-VEC) to close contacts reported in clinical studies to date.

Small amounts of talimogene laherparepvec (T-VEC) have been detected in patients' blood and urine for up to 1 week after injection. In patients treated with talimogene laherparepvec (T-VEC) in clinical trials, talimogene laherparepvec (T-VEC) has been found on the surface of the injected tumors, into the second week after the injection, but not on the outside of the dressings that covered these injection sites. Close contacts should avoid direct contact with the injection sites.

It is not known if talimogene laherparepvec (T-VEC) virus can appear in mucous membranes of the lips and mouth or genitals of treated patients. A clinical study is ongoing to determine if talimogene laherparepvec (T-VEC) can be detected in the mouth area and genital area of treated patients.

To reduce the risk of exposure to and transmission of talimogene laherparepvec (T-VEC), please read carefully the Instructions below.

III. Who Should Not Have Contact with talimogene laherparepvec (T-VEC)?

Persons with weakened immune systems, newborns and pregnant women should not come in contact with the lesions that have been injected with talimogene laherparepvec (T-VEC) or body fluids of treated patients.

Close contacts or family members who are pregnant or have weakened immune systems should not touch injection sites, change dressings or clean injection sites. Newborns should not come into contact with the injection sites. Used dressings and cleaning materials should be kept away from pregnant women, newborns and those with weakened immune systems.

IV. What Precautions Should Be Taken to Avoid Being Exposed to talimogene laherparepvec (T-VEC)?

- Avoid direct contact with the treated patient's injection sites and body fluids.
- Wear gloves if changing dressings which cover the treated patient's injection sites.
- Place all used dressings and cleaning materials in a sealed, plastic bag, and throw them away as household waste or return to the study site for disposal depending on local guidance.
- The patient should avoid touching or scratching the injection site.
- The injection sites should be covered for at least 7 days after the last injection with watertight dressings which allow for air exchange. If the dressing comes loose or falls off prior to 7 days after the injection, it should be replaced right away with a clean dressing. However, you may need to keep the dressing on longer if the lesions at the injection sites are weeping or oozing. (please also refer to **Instructions for talimogene laherparepvec (T-VEC) Injection Site Care**)
- Observe proper hygiene (wash hands with warm water and soap after touching the injected lesions or handling the dressings) to avoid spreading talimogene

laherparepvec (T-VEC) to other persons. If there is direct contact with the injected sites, you should clean the affected area on your body with soap and water and/or a disinfectant.

- If the treated patient develops any mouth or genital herpetic lesions (for example a painful fluid filled blister) during treatment with talimogene laherparepvec (T-VEC) or during the follow-up period of the clinical trial, they should avoid activities that could increase the possibility of transmission such as sharing straws, drinking glasses or engaging in sexual activity until the lesions fully resolve.
- The naturally occurring herpes simplex virus (HSV-1) can be transmitted through sexual contact. It is not known if talimogene laherparepvec (T-VEC) will behave the same way, thus treated patients or their partners should use a latex condom when engaging in sexual activity to prevent possible transmission of talimogene laherparepvec (T-VEC) during the treatment with talimogene laherparepvec (T-VEC) and until 4 months after the end of treatment. For those with latex allergies, polyurethane condoms may be used.

V. What Can Happen if Family Members or Close Contacts are Exposed to talimogene laherparepvec (T-VEC)?

The naturally occurring type of HSV can cause a variety of symptoms. Due to the changes in talimogene laherparepvec (T-VEC) that make it different from the naturally occurring HSV, the chance of developing a herpes type infection is low, but you should know how to recognize these symptoms.

If talimogene laherparepvec (T-VEC) were transmitted from a talimogene laherparepvec (T-VEC) treated patients to a third party, the potential symptoms might be similar to those of the naturally occurring herpes simplex virus such as:

- Sores around the mouth (“cold sore”, “fever blister”) or genitals (“genital sore”).
- Blisters may develop on the fingers, ears or face.
- Eye infection (herpetic keratitis) with eye pain, light sensitivity, discharge from the eyes or blurry vision.
- Abdominal pain and infections, and inflammation inside the abdomen (infrequently).
- Rarely, serious infections of the brain (encephalitis) or spinal cord causing paralysis (unable to move) have been reported. Signs may include fever, confusion or other behavior changes, headache, numbness and pain in the legs, constipation or difficulty with urination.
- Life-threatening infections (disseminated herpes) can develop in people with a weakened immune system.
- In addition, after the acute infection, the naturally occurring herpes virus may travel to spinal nerve roots. The virus can reactivate from the nerve roots and cause recurrent cold sores or other signs of infection as described above. Stress, other illness, or menstruation are common triggers for reactivation of the naturally occurring herpes simplex virus.

Persons should seek a healthcare provider for signs of systems suggestive of herpes infection occur. talimogene laherparepvec (T-VEC) is sensitive to the antiviral drug acyclovir and any possible infection may be treated with this drug in its usual doses by your doctor.

VI. INSTRUCTIONS for Reporting of Suspected talimogene laherparepvec (T-VEC) Exposure or Infection:

1) **Instructions for <u>Close Contact</u> with suspected exposure to talimogene laherparepvec (T-VEC)**: If a close contact or non-study HCP

is suspected to have been exposed to talimogene laherparepvec (T-VEC) (e.g. symptoms suggestive of herpes infection or contact of open skin/mucosa with talimogene laherparepvec (T-VEC)), **you should inform the individuals below** and seek medical attention. Your doctor may want to determine if talimogene laherparepvec (T-VEC) is present, depending on the symptoms observed. For example if a cold sore appears, a swab may be taken for analysis. These tests will be most reliable if done within the first 3 days of symptoms occurring, but you should report to your health care provider at any time symptoms appear. Before any samples or information about your health or symptoms is collected your authorization will be requested in writing.

1. **Call the Amgen Call Center** at 1-855-IMLYGIC (1-855-465-9442) immediately when the close contacts/HCP noticed symptoms/signs of herpes infection, as testing of the virus must occur within 3 days**.**
    - Amgen will provide close contacts/HPC with instructions to seek medical consultations for management and potentially for talimogene laherparepvec (T-VEC) DNA test. The talimogene laherparepvec (T-VEC) DNA test must be done within three days of the appearance of the symptoms.
    - The physicians of Close Contacts will be responsible for obtaining the swab of herpetic lesions submit it to talimogene laherparepvec (T-VEC) testing, per instructions from Amgen.
    - The Amgen Call Center is open 24 hours a day, 7 days a week (24/7). Please have this Information Sheet handy when you call Amgen.
2. Also **inform the talimogene laherparepvec (T-VEC) clinical trial doctor** of the incident by contacting: **<<insert study site contact>>.**
3. When seeing a doctor for your symptom or talimogene laherparepvec (T-VEC) exposure, please give this Information Sheet to the Doctor.

18.6 Information Sheet for Patients Receiving Talimogene Laherparepvec (T-VEC)

Study Title: _____

NCI protocol #:_____ Amgen Tracking #:_____

The patient _____ is enrolled on the clinical trial above using the experimental drug **Talimogene laherparepvec (T-VEC)**. This clinical trial is sponsored by the National Cancer Institute.

The PI Name: _____ and PI contact # _____

_____

This form is addressed to the patient, but includes important information for others who care for this patient.

Dear Patient:

This Information Sheet is being provided to patients who has been enrolled in a clinical trial of Talimogene Laherparepvec (T-VEC**).** A separate Information Sheet is also being provided for you close contacts and Healthcare Providers not involved in the trial**.** A close contact is considered a person that lives with the Patient (household member), care-giver, sex partner, or shares a bed with the Patient or conducts other activities that could involve exchange of bodily fluids through close physical contact.

The purpose of this Sheet is to inform you of 1) ***Potential risk of exposure to talimogene laherparepvec (T-VEC)***, 2) ***Precautions*** and 3) ***Instructions in the case of talimogene laherparepvec (T-VEC) transmission***. In the end of this document, additional information is also provided for ***Instructions for talimogene laherparepvec (T-VEC) injected sites care***.

I. What is the Study Drug, Talimogene Laherparepvec (T-VEC)?

talimogene laherparepvec (T-VEC) is an investigational drug that is being studied for the treatment of certain types of cancer. talimogene laherparepvec (T-VEC) contains a weakened form of the Herpes Simplex Virus Type 1 (the "cold sore" virus or "HSV-1").

II. Can talimogene laherparepvec (T-VEC) be spread to family members or other close contacts?

talimogene laherparepvec (T-VEC) could potentially be spread to family or people who have close physical or intimate contact with the Patient after tumor(s) are injected with the study drug. So far there have been no reported cases in clinical trial participants who have received talimogene laherparepvec (T-VEC) of spreading talimogene laherparepvec (T-VEC) to family members or other close contacts. In clinical trials so far, no talimogene laherparepvec (T-VEC) has been detected outside of the dressing that is placed on top of the site where it was injected.

The naturally occurring herpes simplex virus is not transmitted through the air or water droplets (such as when coughing or sneezing). Spreading occurs through direct contact from one person to another, particularly if a cold sore or genital sore is present (for example, through kissing or having sexual intercourse or other intimate contact). It may also be spread by sharing a razor, towel, dish that has come in contact with a sore or bodily fluids.

Spreading (transmission) of talimogene laherparepvec (T-VEC) may be similar to spreading of the naturally occurring herpes simplex virus, and spreading may be more likely if you have a break in your skin or a mucous membrane comes into contact with an injection site or body fluids of a treated patient. Unlike the naturally occurring virus, however, talimogene laherparepvec (T-VEC) is administered into tumor lesions and is not expected to be able to replicate effectively in other noncancerous tissues. There have been no cases of spreading of talimogene laherparepvec (T-VEC) to close contacts reported in clinical studies to date.

Small amounts of talimogene laherparepvec (T-VEC) have been detected in patients' blood and urine for up to 1 week after injection. In patients treated with talimogene laherparepvec (T-VEC) in clinical trials, talimogene laherparepvec (T-VEC) has been found on the surface of the injected tumors, into the second week after the injection, but not on the outside of the dressings that covered these injection sites. Close contacts should avoid direct contact with the injection sites.

It is not known if talimogene laherparepvec (T-VEC) virus can appear in mucous membranes of the lips and mouth or genitals of treated patients. A clinical study is ongoing to determine if talimogene laherparepvec (T-VEC) can be detected in the mouth area and genital area of treated patients.

To reduce the ris***k of exposure to and transmission of talimogene laherparepvec (T-VEC), please read carefully the Instructions below.***

III. Who Should Not Have Contact with talimogene laherparepvec (T-VEC)?

Persons with weakened immune systems, newborns and pregnant women should not come in contact with the lesions that have been injected with talimogene laherparepvec (T-VEC) or body fluids of treated patients.

Close contacts or family members who are pregnant or have weakened immune systems should not touch injection sites, change dressings or clean injection sites. Newborns should not come into contact with the injection sites. Used dressings and cleaning materials should be kept away from pregnant women, newborns and those with weakened immune systems.

IV. What Precautions Should Be Taken to Avoid Being Exposed to talimogene laherparepvec (T-VEC)?

- Avoid direct contact with the treated patient's injection sites and body fluids.
- Wear gloves if changing dressings which cover the treated patient's injection sites.
- Place all used dressings and cleaning materials in a sealed, plastic bag, and throw them away as household waste or return to the study site for disposal depending on local guidance.
- The patient should avoid touching or scratching the injection site.
- The injection sites should be covered for at least 7 days after the last injection with watertight dressings which allow for air exchange. If the dressing comes loose or falls off prior to 7 days after the injection, it should be replaced right away with a clean dressing. However, you may need to keep the dressing on longer if the lesions at the injection sites are weeping or oozing. (please also refer to **Instructions for talimogene laherparepvec (T-VEC) Injection Site Care**)
- Observe proper hygiene (wash hands with warm water and soap after touching the injected lesions or handling the dressings) to avoid spreading talimogene laherparepvec (T-VEC) to other persons. If there is direct contact with the injected sites, you should clean the affected area on your body with soap and water and/or a disinfectant.

- If the treated patient develops any mouth or genital herpetic lesions (for example a painful fluid filled blister) during treatment with talimogene laherparepvec (T-VEC) or during the follow-up period of the clinical trial, they should avoid activities that could increase the possibility of transmission such as sharing straws, drinking glasses or engaging in sexual activity until the lesions fully resolve.
- The naturally occurring herpes simplex virus (HSV-1) can be transmitted through sexual contact. It is not known if talimogene laherparepvec (T-VEC) will behave the same way, thus treated patients or their partners should use a latex condom when engaging in sexual activity to prevent possible transmission of talimogene laherparepvec (T-VEC) during the treatment with talimogene laherparepvec (T-VEC) and until 4 months after the end of treatment. For those with latex allergies, polyurethane condoms may be used.

V. What Can Happen if Family Members or Close Contacts are Exposed to talimogene laherparepvec (T-VEC)?

The naturally occurring type of HSV can cause a variety of symptoms. Due to the changes in talimogene laherparepvec (T-VEC) that make it different from the naturally occurring HSV, the chance of developing a herpes type infection is low, but you should know how to recognize these symptoms.
If talimogene laherparepvec (T-VEC) were transmitted from a talimogene laherparepvec (T-VEC) treated patients to a third party, the potential symptoms might be similar to those of the naturally occurring herpes simplex virus such as:

- Sores around the mouth ("cold sore", "fever blister") or genitals ("genital sore").
- Blisters may develop on the fingers, ears or face.
- Eye infection (herpetic keratitis) with eye pain, light sensitivity, discharge from the eyes or blurry vision.
- Abdominal pain and infections, and inflammation inside the abdomen (infrequently).
- Rarely, serious infections of the brain (encephalitis) or spinal cord causing paralysis (unable to move) have been reported. Signs may include fever, confusion or other behavior changes, headache, numbness and pain in the legs, constipation or difficulty with urination.
- Life-threatening infections (disseminated herpes) can develop in people with a weakened immune system.

In addition, after the acute infection, the naturally occurring herpes virus may travel to spinal nerve roots. The virus can reactivate from the nerve roots and cause recurrent cold sores or other signs of infection as described above. Stress, other illness, or menstruation are common triggers for reactivation of the naturally occurring herpes simplex virus.

Persons should seek a healthcare provider for signs of systems suggestive of herpes infection occur. talimogene laherparepvec (T-VEC) is sensitive to the antiviral drug acyclovir and any possible infection may be treated with this drug in its usual doses by your doctor.

VI. INSTRUCTIONS for Reporting of Suspected talimogene laherparepvec (T-VEC) Exposure or Infection:

1) **Instructions for <u>patients treated with talimogene laherparepvec (T-VEC)</u>:**
If you develop symptoms of herpes infection:

   - **IMMEDIATELY** inform the talimogene laherparepvec (T-VEC) trial doctor by contacting: **<<insert study site contact>>.** The talimogene laherparepvec (T-VEC) trial doctor will provide further instructions for

management and evaluation. You doctor may need to obtain test for the virus within 3 days of your notification of the symptoms

- If you are seeing a doctor who is not part of the clinical trial, please give this information sheet to the Doctor and have them contact the talimogene laherparepvec (T-VEC) trial staff: **<<insert study site contact>>.**

2) **Instructions for Close Contact or non-study Healthcare providers with suspected exposure to talimogene laherparepvec (T-VEC)**:
   - Please refer to the Information Sheet for Close Contacts.

18.7 Instructions for Talimogene Laherparepvec (T-VEC) Injection Site Care

After administration of talimogene laherparepvec (T-VEC) the injected lesions will be covered with a watertight dressing which allows for air exchange and it may also include an absorbent pad underneath covering the lesion. These dressings are like the dressings that are placed on skin when intravenous lines are placed to deliver medicine.

The dressing can be removed 7 days after the last talimogene laherparepvec (T-VEC) injection. However, you may need to keep the dressing on longer if the lesions at the injection sites are weeping or oozing. Patients and/or caregivers must be instructed to change the dressings properly, and they should be provided with all necessary materials including disposable gloves, dressings, and plastic containers or bags. When you remove the dressing follow the instructions below:

1) Wash your hands thoroughly with soap and water.

2) Put on the disposable gloves, gently remove the dressing and place the soiled dressing in the disposal bag provided.

3) Take the disposable gloves off by turning inside out and put them in the disposal bag. Seal the plastic bag and throw away as household waste or return to the study site for disposal depending on local guidance.

4) Wash your hands thoroughly with soap and warm water.

If the dressing becomes loose or comes off altogether prior to 7 days from the injection site, you will need to change the dressing. You will be provided with extra dressings. You may need a relative or friend to help change the dressing. When you change the dressing, follow the instructions below:

1) Lay out all the necessary supplies, such as, alcohol swabs, new dressing and a plastic bag to place the soiled dressing.

2) Wash hands thoroughly with soap and warm water, and put on the disposable gloves prior to changing the dressing.

3) Remove the soiled dressing and place it into the plastic bag or container.

4) Before placing a new dressing, change gloves by turning them inside out and put them into the disposal bag.

5) Next, put on a fresh pair of gloves

6) Apply the new dressing as instructed. Try to avoid touching the injection site while applying the new dressing.

7) Wipe down the outside of the dressing with an alcohol swab to further minimize any cross contamination.

8) Take off the gloves and place all soiled materials in the disposal bag.

9) Seal the plastic bag and dispose as household waste or return to the study site for disposal depending on local guidance.

10) Wash your hands thoroughly with soap and warm water.

If your close contact (household members, care-givers, sex partners, or someone you share a bed with) is pregnant or has a weakened immune system, they should not touch injection sites, change your dressings or clean your injection sites. Newborns (babies who are one month or less in age) should not come into contact with the injection sites. Keep used dressings and cleaning materials away from pregnant women, newborns, and those with weakened immune systems.

IMPORTANT

- Reactions at or near the area of the injection have been seen in people administered talimogene laherparepvec (T-VEC). Symptoms include bleeding, redness, swelling and inflammation at the injection site. Skin infection caused by bacteria at the site of injection which may require hospitalization for antibiotic treatment have also been reported. Other symptoms may include warmth at the injection site or symptoms of delayed wound healing at or around the injection site such as injection site discharge, foul odor, or dead tissue at the injection site. If you notice symptoms of delayed wound healing, such as those mentioned above, at the injection site(s), you should contact the study doctor or his/her staff immediately.

- If there are signs that the skin (under the dressing but that was not injected and is in contact with the adhesive) is becoming irritated/red, please contact the study site. A different dressing type may need to be applied or you may have a cream applied that helps prevent irritation.

Do Not:

- Don't put salves or ointments on the injection site.

- Don't scratch or pick at the injection site

- Avoid directly touching (with bare hands) uncovered skin that has been injected with the study drug.

Infections: Tumor necrosis may be seen with the use of talimogene laherparepvec (T-VEC). The presence of necrotic or ulcerating lesions may pre-dispose the patient to local and/or systemic infections such as cellulitis, bacteremia, etc. Careful wound care and infection precautions are recommended if tumor necrosis results in open wounds. Patients should avoid touching or scratching injection sites or their occlusive dressings, as doing so could lead to inadvertent transfer of IMLYGIC to other areas of the body.

18.8 Information Related to Exposure to Talimogene Laherparepvec (T-VEC)

Accidental Occupational Exposure:

Accidental exposure may lead to transmission of talimogene laherparepvec (T-VEC) and herpetic infection. Nurses and other study staff (e.g., pharmacists) with open skin wounds should not come into direct contact with talimogene laherparepvec (T-VEC). HCP who are immunocompromised or pregnant should not prepare or administer talimogene laherparepvec (T-VEC). All personnel handling the virus or material contaminated with talimogene laherparepvec (T-VEC) must observe safety precautions (e.g., wear a laboratory coat, safety glasses, and gloves).

- In the event of an accidental occupational exposure through a splash to the eyes or mucous membranes, flush with clean water for at least 15 minutes. In the event of exposure to broken skin or needle stick, clean the site thoroughly with soap and water or a virucidal disinfectant such as 1% sodium hypochlorite or Virkon®.

Exposure of Non-treated Individuals to talimogene laherparepvec (T-VEC):

As there is a potential risk for exposure of talimogene laherparepvec (T-VEC) from patients to anyone in direct contact with the patient, persons with open skin lesions or who are immunosuppressed, pregnant women and newborns should avoid direct contact with the injected lesions, dressings or body fluids of the treated patients.

- In the event of a secondary exposure (e.g., leakage through occlusive dressing to patient or contacts) to talimogene laherparepvec (T-VEC), clean the site thoroughly with soap and water or a virucidal disinfectant such as 1% sodium hypochlorite or Virkon®.

Persons should seek a healthcare provider for signs of systemic (fever, aches, nausea, and malaise) or local (fever, pain, redness and swelling) infection. talimogene laherparepvec (T-VEC) is sensitive to acyclovir which may be administered, if clinically indicated.

Accidental Spills:

Spills should be treated with a virucidal agent. All disposable materials contaminated with talimogene laherparepvec (T-VEC) must be destroyed and disposed of in compliance with local institutional guidelines.

18.9 Receiving Instructions for NCI-supplied Talimogene laherparepvec (NSC 785349)

IMPORTANT: READ THE ENTIRE INSTRUCTIONS BEFORE OPENING THE INNER SHIPPING CONTAINER

Step 1: Verify all shipment documents are present:
- NCI Shipment Record of Clinical Drug Request
- Temperature Exposure Log

Step 2: Transfer Talimogene laherparepvec vials to -80°C (+/- 10^0 C) freezer

You have 90 seconds to verify the contents of the shipping container and place the agent supplies in the -80°C (+/- 10^0 C) freezer once the inner container lid is opened and the supply exposed to room temperature.

- Place the shipping container near the -80°C (+/- 10^0 C) freezer
- Don gloves per your institutional procedures for handling dry ice
- Open the lid of the inner shipping container
- A second person should record the start time on the temperature exposure log once the lid of inner shipping container is removed
- Open the payload box sleeve and remove the payload box containing the carton(s) of Talimogene laherparepvec
- Open the payload box and remove carton(s) of Talimogene laherparepvec
  - Verify agent, strength, quantity and lot number received against NCI Shipment Record of Clinical Drug Request
- Place carton(s) of Talimogene laherparepvec in the -80oC (+/- 100 C) freezer and close the freezer door
- Record the stop time on the temperature exposure log

Step 3: Complete documentation
- Confirm the time difference from start time to stop time does not exceed 90 seconds
- Complete remainder for temperature exposure log and retain with your study records
- If exposure time exceeds 90 seconds, quarantine the agent supplies in the -80oC (+/- 100 C) freezer and call PMB immediately at 240-276-6575 for guidance.

18.10 NCI Temperature Exposure Log Talimogene laherparepvec (NSC 785349)

NCI Protocol Number: _____

PMB Order Number: _____ (obtain from Shipment Record)

Date Received: _____

Maximum exposure time: **90 Seconds**
Exposure Time
Start Time = time inner shipping container lid is removed
Stop Time = time -80°C (+/- 10^0 C) freezer door is closed

Start Time: _____:_____:_____ (hour:minute:second - example: 09:50:01)
Stop Time: _____:_____:_____ (hour:minute:second - example: 09:50:58)

Confirm time difference from start time to stop time does not exceed 90 seconds:
□ YES □ NO

Comments: _____

Name: _____ Date: _____

Complete one log for each shipping container received.

Retain log with your study records. If exposure time exceeds 90 seconds, quarantine the agent supplies in the -80°C (+/- 10^0 C) freezer and call PMB immediately at 240-276-6575 for guidance.