MSK PROTOCOL COVER SHEET

Phase II study of talimogene laherparepvec (T-VEC) administered concurrently with the anti-PD1 monoclonal antibody pembrolizumab in patients with metastatic and/or locally advanced sarcoma.

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

A phase II study of talimogene laherparepvec (T-VEC) administered concurrently with the anti-PD1 monoclonal antibody pembrolizumab in patients with metastatic and/or locally advanced sarcoma.

Sarcomas comprise a very diverse group of malignancies including more than 50 subtypes of bone and soft tissue origin. Despite optimal approach, approximately 25-50% of patients will develop recurrent and metastatic disease after receiving initial therapy with curative intent. In this setting, responses to standard cytotoxic chemotherapy occur in 10-30% of the cases and median survival is 10-18 months.
Sarcomas are immunogenic neoplasms with a need for more therapeutic options. Prior immunotherapeutic agents have shown promise in select sarcoma patients. Using a combination of talimogene laherparepvec (T-VEC) administered intralesionally concurrently with the anti-PD1 monoclonal antibody pembrolizumab to treat patients with sarcomas and our planned scientific correlates, we believe we can assess the safety and efficacy of immune activating therapy and better understand the effects of combined therapy in antitumoral immune response.
This is a single-center, phase II study to evaluate the efficacy of the oncolytic herpes virus talimogene laherparepvec, given in combination with pembrolizumab for patients with metastatic and/or locally advanced sarcomas.

Patients will initiate treatment with talimogene laherparepvec given intralesionally and pembrolizumab. Talimogene laherparepvec treatment will be given at Day 1 Week 1, 4, and every 3 weeks thereafter. (Table 1). Pembrolizumab will be given at Day 1 week 1 and every 3 weeks thereafter (Table 1). Patients will be reassessed at week 8 and every 8 weeks thereafter. Treatment will be repeated until the patient develops progressive disease, unacceptable toxicity or for up to 12 months.

Table 1. Study design and treatment plan

Design	Talimogene laherparepvec	Pembrolizumab
One stage design	Intralesionally: Up to 4mL at 10^6 pfu/mL at Week 1 Up to 4mL at 10^8 pfu/mL starting at Week 4 and every 3 weeks.	Dose: 200mg/dose at Week 1, and every 3 weeks thereafter.

This phase II study will be conducted using a one-stage design, based on the exact binomial test.

The primary objective of this study is to evaluate the efficacy, as assessed by the best objective response rate (complete response + partial response) at 24 weeks by RECIST 1.1, of talimogene laherparepvec in combination with pembrolizumab in patients with metastatic and/or locally advanced sarcoma. Secondary objectives are to assess the safety/tolerability of the treatment, to determine PFS rate at 24 weeks and OS and to evaluate the efficacy, as assessed by irRECIST. The study will accrue a maximum of 20 patients in a single stage

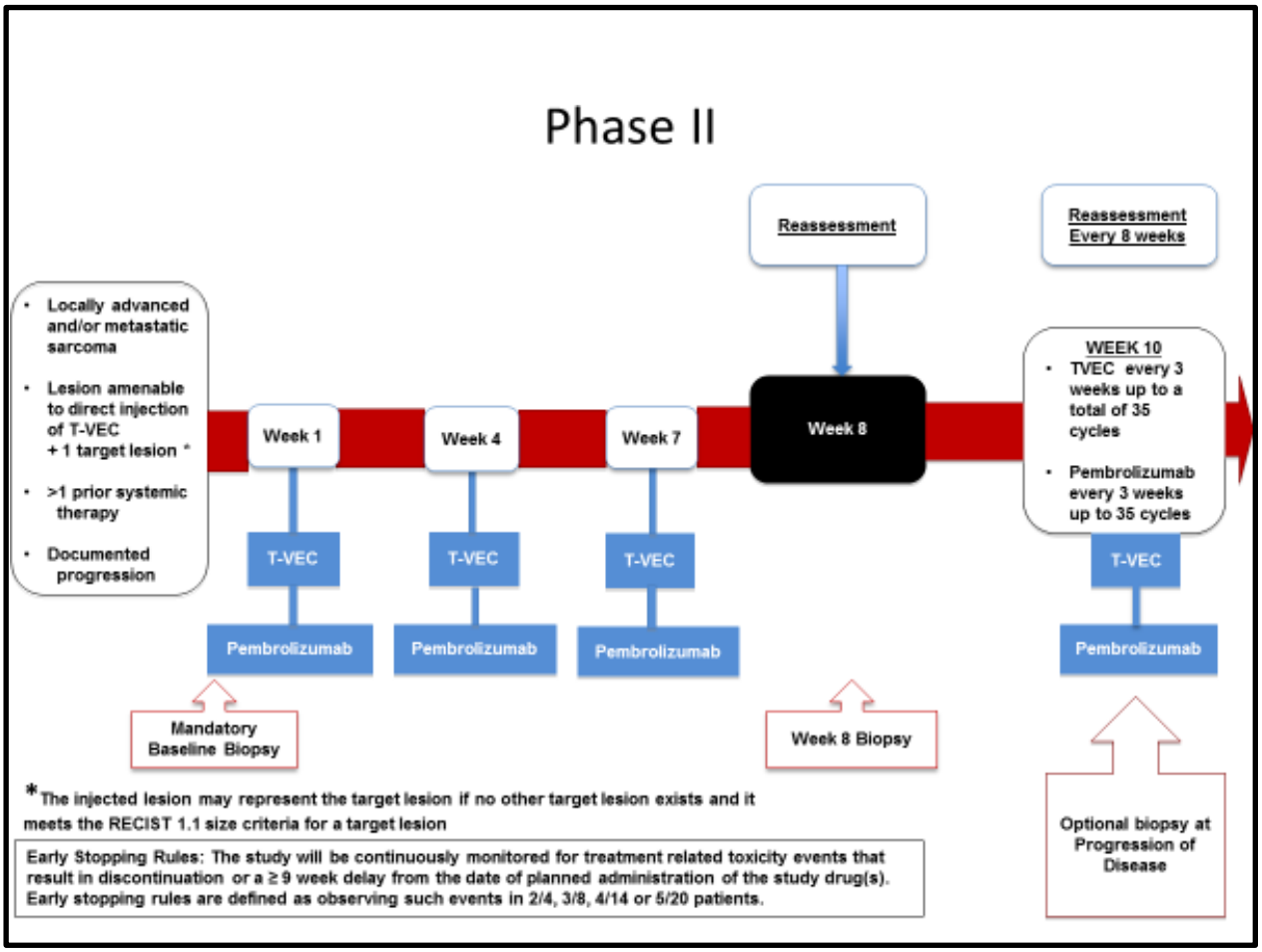
design, with sequential monitoring for predefined treatment-related toxicities. Toxicity will be recorded using CTCAE v.4.03.

All patients enrolled in this study will undergo biopsies at baseline and week 8 where feasible. Optional biopsies at progression will be offered. Biopsies will be done of both the lesion injected with talimogene laherparepvec and one additional target lesion, if technically feasible. Serial blood samples will be obtained at baseline, during, and after treatment. The trial schema is outlined below **(Figure 1)**.

Exploratory objectives include:

I. To investigate the rate of seroconversion in patients HSV seronegative at baseline after initial intralesional infusion of talimogene laherparepvec
II. To evaluate associations between selected biomarkers measured in serial peripheral blood and with clinical efficacy, including immunophenotyping and Functional Analyses, evaluation of serum levels of chemokines, cytokines and other immune mediators, and characterization of T-cell receptor clonality in peripheral blood.
III. To assess the potential effect of talimogene laherparepvec cell lysis and pembrolizumab on selected biomarker expression measured in pre- and post-treatment tumor tissue and the association between these biomarkers and with clinical outcome, including characterization of PD-1/PD-L1 expression, tumor infiltrating lymphocytes (TILs) and tumor antigens, gene expression profiling, and characterization of T-cell receptor clonality in tumor-infiltrating lymphocytes (TIL).
IV. To evaluate the association between baseline tumor mutational burden and neoantigen production with clinical efficacy of the study therapy.

Figure 1A. Trial overview.



Additional Cohorts:

Following enrollment of the first 20 patients on this study additional cohorts will open. The additional cohorts will evaluate the efficacy and safety of T-VEC in combination with pembrolizumab in an additional 40 patients. The additional cohorts will enrich for sarcoma histological subtypes where the combination study therapy demonstrated activity in the initial 20 patients enrolled on the study including cutaneous angiosarcoma, epithelioid sarcoma, undifferentiated pleomorphic sarcoma and myxofibrosarcoma. The additional cohorts will consist of 3 cohorts of 10 patients. A metastatic/inoperable locally advanced sarcoma group (n=30) will consist of 3 cohorts of 10 patients each, based on histological subtype including epithelioid sarcoma (n=10), cutaneous angiosarcoma (n=10) and UPS/MFS (n=10)

Patients enrolled metastatic/locally advanced cohort with inoperable disease will be treated in the same way as outlined above for the original 20 patients who were enrolled on the study.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Objectives
Primary objective: To evaluate the efficacy, as assessed by the best objective response rate (complete response + partial response) at 24 weeks by RECIST 1.1, of talimogene laherparepvec in combination with pembrolizumab in patients with advanced sarcoma.

Secondary objectives:

1. To assess the feasibility of pembrolizumab in combination with talimogene laherparepvec as determined by study completion to facilitate efficacy assessment without early termination due to excessive treatment-related toxicities.
2. To assess the safety of talimogene laherparepvec in combination with pembrolizumab in patients with advanced sarcoma using CTCAE v4.03 criteria for toxicity assessment
3. To determine the progression free survival (PFS) rate at 24 weeks by RECIST 1.1 and irRECIST, and overall survival (OS) for patients treated with talimogene laherparepvec in combination with pembrolizumab.

4. To evaluate the efficacy, as assessed by the best objective response rate (complete response + partial response) at 24 weeks by immune-related response criteria (irRECIST), of talimogene laherparepvec in combination with pembrolizumab in patients with advanced sarcoma.

Exploratory objectives and correlative studies:

I. To investigate the rate of seroconversion in patients HSV seronegative at baseline after initial intralesional infusion of talimogene laherparepvec
II. To evaluate associations between selected biomarkers measured in serial peripheral blood with clinical efficacy, including immunophenotyping and functional analyses, evaluation of serum levels of chemokines, cytokines and other immune mediators, and characterization of T-cell receptor clonality in peripheral blood.
III. To assess the potential effect of talimogene laherparepvec cell lysis and pembrolizumab on selected biomarker expression measured in pre- and post-treatment tumor tissue and the association between these biomarkers and with clinical outcome, including characterization of PD-1/PD-L1 expression, tumor infiltrating lymphocytes (TILs) and tumor antigens, gene expression profiling, and characterization of T-cell receptor clonality in tumor-infiltrating lymphocytes (TIL).
IV. To evaluate the association between baseline tumor mutational burden and neoantigen production with clinical efficacy of the study therapy.

<u>Additional Cohorts: Primary and Secondary Objectives</u>

Locally advanced/metastatic cohorts

Primary objective: To estimate the efficacy, as assessed by the best objective response rate (complete response + partial response) at 24 weeks by RECIST 1.1, of talimogene laherparepvec in combination with pembrolizumab in each sarcoma subtype-specific cohort [(i) UPS/myxofibrosarcoma, (ii) epithelioid sarcoma and (iii) cutaneous angiosarcoma]

Secondary objectives:

1. To assess the safety of talimogene laherparepvec in combination with pembrolizumab in patients with advanced sarcoma using CTCAE v4.03 criteria for toxicity assessment

2. To determine the progression free survival (PFS) rate at 24 weeks by RECIST 1.1 and irRECIST and overall survival (OS) for patients in each sarcoma subtype-specific cohort treated with talimogene laherparepvec in combination with pembrolizumab..

3. To evaluate the efficacy, as assessed by the best objective response rate (complete response + partial response) at 24 weeks by immune-related response criteria (irRECIST), of talimogene laherparepvec in combination with pembrolizumab in each sarcoma-subtype specific cohort.

Additional Cohorts: Exploratory Objectives

Exploratory objectives:

1. To evaluate associations between selected biomarkers measured in serial peripheral blood with clinical efficacy, including immunophenotyping and functional analyses, evaluation of serum levels of chemokines, cytokines and other immune mediators, and characterization of T-cell receptor clonality in peripheral blood.

2. To assess the potential effect of talimogene laherparepvec cell lysis and pembrolizumab on selected biomarker expression measured in pre- and post-treatment tumor tissue and the association between these biomarkers and with clinical outcome, including characterization of PD-1/PD-L1 expression, tumor infiltrating lymphocytes (TILs) and tumor antigens, gene expression profiling, bulk RNA sequencing to define the immune infiltrate, single cell RNA sequencing of TILs, and characterization of T-cell receptor clonality in tumor-infiltrating lymphocytes (TIL).

3. To evaluate the association between baseline tumor mutational burden and neoantigen production with clinical efficacy of the study therapy.

4. To evaluate the potential for noninvasive imaging modalities including photography, confocal microscopy, optical coherence tomography, and ultrasound for the purposes of monitoring and/or predicting response to therapy in patients with cutaneous disease

3.0 BACKGROUND AND RATIONALE

3.1 Sarcomas – unmet need for new therapies.

Sarcomas correspond to a heterogeneous group of mesenchymal neoplasms of bone and soft tissue origin characterized by more than 50 distinct subtypes. Approximately 13,000 cases of soft tissue and bone sarcomas are diagnosed annually in the US. Surgery is the mainstay of therapy for localized sarcoma, and adjuvant radiation therapy and chemotherapy are used in very particular situations. Despite primary combined modality therapy, between 25-50% of patients develop recurrent and/or metastatic disease.[1,2] Complete responses to chemotherapy for recurrent or metastatic sarcoma are rare, and median survival in the metastatic setting is 10-18 months.[3,4] Standard cytotoxic chemotherapy agents such as

doxorubicin, ifosfamide, and dacarbazine result in objective responses in 10-30% of the patients, and this is significantly influenced by histologic variant.[5] The development of novel and effective therapies is desperately needed for patients with advanced/metastatic sarcomas.

3.2 Sarcoma: an immunogenic tumor

Immunotherapeutic strategies may be a promising approach to treating this disease. The role of the immune system as a mechanism of cancer therapy was first observed in a sarcoma patient who had a response after an erysipelas infection.[6] Sarcomas are more common in patients who are immunosuppressed.[7] Infiltration of lymphocytes has been demonstrated in sarcomas.[8] Furthermore, tumor-infiltrating lymphocytes have been associated with improved survival in Ewing's sarcoma and GIST.[9-12] Spontaneous regression of primary tumors have been seen in desmoid tumors and osteosarcomas.[13,14] There have been multiple clinical trials evaluating the role of immune stimulants such as IL-2, interferon, and liposomal-muramyl tripeptide phosphatidylethanolamine showing some benefit in sarcoma patients.[15-21] T cells genetically engineered to target NY-ESO-1 expressing synovial sarcoma have shown some promise.[22] In patients with GIST, tyrosine kinase inhibitors such as imatinib can have stimulating effects on multiple immune cells.[12]

3.3 Oncolytic immunotherapy in sarcomas: inducing direct antitumoral effect through cell lysis and stimulating antigen-directed immune response.

Although the role of viruses in treatment of cancer has long been studied, only recently the incorporation of gene engineering techniques has allowed significant improvements in the antitumoral activity of replicating viruses. Advances in molecular biology and recombinant DNA technology allowed for the development of viruses with genetically altered, highly specific cytolytic properties. As a result, oncolytic virotherapy has led to promising results in the management of several malignancies.[23-25] In addition to direct cytopathic effects caused by intracellular viral replication (oncolysis); genetic manipulation has allowed the development of strains capable of increasing cytotoxic activity and enhancing antitumoral immune responses mediated by transcription products from engineered viral genome. Furthermore, both cellular and humoral immune responses have been documented following administration of oncolytic viruses.[26-29] In the preclinical setting, direct intratumoral injections of oncolytic viruses have been shown to induce tumor regression in a variety of syngeneic and xenograft ed rodent tumor models. Interestingly, unilateral injection of oncolytic herpesvirus in mice bearing bilateral tumors resulted in regression of distant lesions and further resistance to subsequent tumor inoculation, coupled with the expression of cell-specific cytotoxic T lymphocytes.[30-31] To further develop this concept, a variety of strains have been engineered to express different immunostimulatory molecules, including cytokines (IL-2, IL-12, GM-CSF), tumor-associated antigens, co-stimulatory proteins (CD80 and CD40 ligand) and chemokines. Following the documentation of antitumoral activity in neural neoplasms, ovarian cancer, melanoma and other epithelial malignancies, [25] oncolytic viruses were also studied in sarcoma tumor cells. Different strains of adenovirus, herpesvirus, vaccinia and RNA viruses have been shown to be able to infect sarcoma cells and result in antitumoral effect.[25, 32, 33] For example, studies with adenoviruses showed their ability to infect and replicate in multiple bone and soft tissue sarcoma cell lines[32] and it was recently shown to be well tolerated in a Phase I trial of patients with advanced solid tumors including sarcomas.[33] Ewing sarcoma panels were tested for adenoviral receptors and were found to be receptive to adenoviral replication and cytotoxicity.[34, 35] After Phase I studies confirmed safety,[36] Phase II studies were designed with

concurrent chemotherapy and confirmed *in vivo* viral replication and anti-tumor activity in sarcoma patients.[37] Similar findings were reported in studies with Vaccinia, Reovirus and other RNA viruses.[38, 39]

In this setting, herpesviruses showed some potential advantages. Herpes simplex virus-1 (HSV) is a large, double-strand DNA, enveloped virus. Modern engineering techniques allowed the genetic manipulation of HSV and elimination of the ICP34.5 gene responsible for neurovirulence, without compromising its infectivity and replication capabilities.[40] Its large genome makes it more amenable to incorporation of therapeutic transgenes. *In vitro*, HSV strains G207 and NV1020 were capable of infecting multiple sarcoma cell lines, including malignant fibrous histiocytoma, rhabdomyosarcoma and osteosarcoma, [41] and also were able to induce complete cytopathic effects in specific subsets. Further investigations revealed that similarly designed viruses induced regression in rhabdomyosarcoma xenografts, [42] with enhanced antitumoral activity when combined with vincristine, and in malignant peripheral nerve sheath tumors (MPNST).[43]

As previously shown, engineered oncolytic herpesviruses have been tested and showed activity in sarcoma cell lines and xenograft models and are currently under clinical development.[44]

3.4 Talimogene laherparepvec: an oncolytic immunotherapy derived from HSV-1 with documented activity in other malignancies.

3.4.1 A brief overview of talimogene laherparepvec

Talimogene laherparepvec (T-VEC, formerly named OncoVEX) is an intralesionally delivered oncolytic immunotherapy derived from herpes simplex virus type-1 (HSV-1) that is deleted for the neurovirulence factor ICP34.5. The genes encoding ICP34.5 are replaced by the coding sequence for human GM-CSF, resulting in its ability to selectively replicate within tumors and to produce GM-CSF to enhance systemic antitumor immune responses after virus replication.[45, 46] Since herpes simplex viruses have the advantage of induced direct cytolytic effect, talimogene laherparepvec exhibits a unique mechanism that combines direct lysis of tumor cells with adaptive immune system stimulation.

3.4.2 Clinical experience with talimogene laherparepvec (IMLYGIC®)

In a phase I trial with multiple refractory malignancies (melanoma, breast, gastrointestinal and head and neck), intralesional talimogene laherparepvec resulted in HSV-antigen-associated tumor necrosis and disease stabilization, including 2 patients with melanoma.[47] Treatment was well tolerated and most side effects were reactions at the injected tumor sites. Pyrexia and flu-like constitutional symptoms were also reported. The promising results prompted a phase II trial to investigate the clinical efficacy of talimogene laherparepvec in patients with stage IIIC and IV melanoma. Intratumoral talimogene laherparepvec was administered at a dose of 4ml of 10^6 pfu/ml followed 3 weeks later by up to 4ml of 10^8 pfu/ml and then every 2 weeks, up to 24 treatments (infusions). The overall response rate was 26%, including 8 complete responses and 5 partial responses. Interestingly, responses occurred in both injected and distant metastatic sites, including liver, lungs and lymph nodes. Treatment was well tolerated.[48]

In an open-label, randomized, phase III trial initially presented at ASCO 2013, talimogene laherparepvec compared to GM-CSF resulted in significant antitumoral activity in 436 patients with advanced melanoma.[49] Talimogene laherparepvec was administered intralesionally (subcutaneously or intranodally). The primary outcome measure was durable

response rates (DRR) defined as the percentage of patients with response rates lasting 6 months or more at any time in their treatment course. This trial met its primary endpoint of a statistically significant improvement in durable response rates; 26% of the patients achieved objective responses, including 11% with complete responses and 16 % who had durable responses. Responses occurred in injected, non-injected and visceral lesions. Initial survival analysis of the OPTiM trial were recently presented; although the difference did not reach statistical significance, an increase of 4.4 mos in overall survival with talimogene laherparepvec was observed (p =0.051; HR 0.787). Median OS was 23.3mos with talimogene laherparepvec vs 18.9mos with GM-CSF. The most common side effects in the OPTiM study were chills (talimogene laherparepvec, 49%; GM-CSF, 9%), pyrexia (43%; 9%), injection-site pain (28%; 6%), nausea (36%; 20%), influenza-like illness (30%; 15%), and fatigue (50%; 36%).Grade ≥ 3 adverse events occurred in 36% of subjects receiving talimogene laherparepvec and 21% of subjects receiving GM-CSF. The only grade 3/4 adverse events occurring in ≥ 5 subjects was cellulitis (talimogene laherparepvec, n=6 [2.1%]; GM-CSF, n=1 [<1%]). Of 10 fatal adverse events in the talimogene laherparepvec arm, eight were attributable to disease progression. The remaining two fatal adverse events (sepsis in the setting of salmonella infection; myocardial infarction) were not considered treatment-related per investigator [49]Final planned overall survival analysis suggested a trend towards improved survival, although the difference did not reach statistical significance (median OS 23.3m vs 18.9m; p=0.0494).[49]

Additional insights into the mechanism of talimogene laherparepvec induced response provide further basis for the combination of talimogene laherparepvec with immunomodulatory agents. In a secondary analysis of the phase II clinical trial published by Kaufman and colleagues, the analysis of effector T cells in tumor samples of melanoma patients treated in the phase II talimogene laherparepvec trial suggested an antigen-specific effector T cell response induced by talimogene laherparepvec. CD8+ T cells derived from peripheral blood specimens revealed a significant increase in MART-1 response, indicating development of systemic antigen-specific antitumor immunity. In addition, vaccination induced downregulation of regulatory T lymphocytes at the tumor sites of responding patients.[50] In addition it has been demonstrated in vitro that GM-CSF induces production of proinflammatory cytokines, by human T lymphocytes and antigen presenting cells, including IL-12, TNFα and IFN-γ. It is also associated with recruitment and expansion of dendritic cells, macrophages and granulocytes and differentiation of monocytes into dendritic cells.[51, 52]

As a result, antigen release and proinflammatory effects induced by GM-CSF production by talimogene laherparepvec could be further amplified by concurrent administration of immune checkpoint inhibitors and enhance antitumoral activity in a synergistic mechanism.

3.5 Tackling different steps in the immune activation cascade to enhance antitumoral immune responses: a possible role for combining oncolytic therapy with immune checkpoint blockade.

As highlighted before, lysis of cells infected by oncolytic viruses not only leads to direct antitumoral effects, but also results in the exposure of tumor-associated antigens to circulating antigen-presenting cells,[53] suggesting a conceptual model in which oncolytic viruses in association with immune checkpoint blockers could further enhance the anti-tumoral activity.[54-61] In mouse models, infection of cells by HSV-1716 resulted in increased expression of molecules associated with dendritic cells maturation and increased cross-presentation of antigens.[53]

A key issue in T-cell mediated antitumoral effect is redirecting immune activity against specific antigens and allowing a synergistic interaction to enhance immune responses. Since the first step in the activation of anticancer immune responses involves the processing of tumoral neoantigens by dendritic cells,[62] antigens release by tumor cells could initiate or reinitiate a self-sustaining process in the setting of immune checkpoint blockade.

T cell activation requires a dual signaling.[63, 64] the binding of the T cell receptor to antigens presented by antigen presenting cells via major histocompatibility complex I and II is the first required signal in T cell activation. Subsequently, the second signal is generated by specific molecules which bind to co-stimulatory receptors in T cells. This signaling leads to T cell proliferation, cytokine release and upregulation of the immune response. As a result of T cell activation, several negative regulators of T cells become overexpressed as a mechanism to prevent autoimmunity and tolerance to self antigens. *Cytotoxic T-lymphocyte-associated protein 4* (CTLA-4) and *programmed cell death 1* (PD-1) are examples of inhibitory T cell receptors. Blockade of CTLA-4 and PD-1 has shown promising results in the treatment of melanoma and other malignancies, with clinical trials demonstrating antitumoral activity and durable responses.[65-67]

Strategies combining different steps of the immune activation cascade have been proved a promising and safe approach. Using melanoma murine models, Zamarin et al. demonstrated that intralesional injection of a oncolytic Newcastle disease virus (NDV) in combination with systemic CTLA-4 blockade was able to induce lymphocytic infiltrates and antitumor effects in distant (non-virally injected) lesions mediated by infiltration by CD8+ and CD4+ effector T cells.[68] In a randomized phase II trial, the ant-CTLA-4 antibody ipilimumab combined with subcutaneous GM-CSF resulted in improved overall survival (HR 0.65; stratified log rank p1=0.016, p2=0.033) in patients with melanoma.[69] Interestingly, a trend toward improved tolerability was noted in the combination arm versus ipilimumab monotherapy. talimogene laherparepvec has also been combined with ipilimumab in patients with advanced melanoma. In a phase 1b/2 trial presented at the ASCO meeting in 2014, talimogene laherparepvec was given by intralesional injection to 18 patients at weeks 1, 4 and then every 2 weeks in association with ipilimumab every 3 weeks starting at week 6 (clinical trial number NCT01740297).[70] Only 2 patients had possible immune-related grade 3 or 4 adverse events. Correlative studies showed increased activated CD8+ T-cells during talimogene laherparepvec + Ipilimumab treatment.[70]

As previously mentioned, PD-1 receptor is another promising potential immunological target. Similar to ipilimumab, this is an immune checkpoint receptor that is expressed by activated T cells. PD-1 is a member of the CD28 family of T-cell costimulatory receptors that also includes CD28, CTLA-4, ICOS and BTLA.[71] PD-1 is expressed on activated T cells, B cells and myeloid cells.[72] There are 2 ligands, *programmed cell death ligands* 1 and 2 (PD-L1 and PD-L2) that are specific for PD-1; PD-L1 is frequently expressed within the tumor microenvironment. Once they bind to PD-1, down-regulation of T-cell activation occurs.[73, 74] When the PD-1 ligand binds to the receptor, the T cell activation is blocked. If this interaction is interrupted, the checkpoint is turned off and antitumor T-cell activation may get enhanced. Indeed, inhibitory antibodies targeting PD-1 and PD-L1 have demonstrated objective responses in multiple tumor types including melanoma. In a study that enrolled and treated 296 patients with nivolumab, a monoclonal antibody targeting PD-1, response rates were 18%, 28% and 27% in patients with non-small cell lung cancer, melanoma and renal cell carcinoma, respectively.[75] There was initial evidence that PD-L1 expression could correlate with clinical activity of PD-1 blockade, suggesting PD-L1 expression as one possible biomarker of response. These data prompted interest in exploring PD-L1 expression in sarcoma. Our

group has demonstrated very high PD-L1 expression in nearly 65% of sarcoma cell lines tested, including synovial sarcoma, Ewing sarcoma, rhabdomyosarcoma, liposarcoma, malignant peripheral nerve sheath tumors, desmoplastic small round cell, osteosarcoma and chondrosarcoma. We then evaluated PD-L1 expression in 50 sarcoma tumor specimens of various subtypes. Immunohistochemistry (IHC) was performed on tumor specimens using a Qualtek monoclonal antihuman PD-L1 antibody (clone 28-8) and an automated assay developed by Dako. We identified ≥1% PDL-1 expression in 6/50 (12%) of samples. There was evidence of macrophage and lymphocyte infiltration both within the tumor and in its surrounding tissue. In a recent study presented at ASCO, Movva and colleagues reported high rates of PD-L1 in liposarcomas and chondrosarcomas.[76]

The combination of talimogene laherparepvec and the anti-PD-1 inhibitory antibody, pembrolizumab, has been explored in the phase Ib setting of patients with unresectable, stage IIIB/IV, treatment naive melanoma. talimogene laherparepvec (≤4mL) was injected into cutaneous, subcutaneous, or nodal lesions: 10^6 PFU/mL day 1, 10^8 PFU/mL day 22 then every 2 weeks thereafter. Pembrolizumab was added from day 36 at 200mg IV every 2 weeks. The trial enrolled 21 patients. No dose limiting toxicities were reported. All 21 patients experienced a treatment-related adverse event (TEAE). The TEAE rate was 19%; G3 TEAE rate was 29%, there were no G4 TEAEs. The most common TEAEs were rash (57%), pyrexia (38%), fatigue (29%), chills (24%), nausea (19%), pruritis (19%), diarrhea (19%), vomiting (14%), headache (14%), and arthralgia (14%). The only G3 TEAEs occurring in >1 patient were anemia (n=2) and rash (n=2; 1 macular and 1 general rash, both following first pembrolizumab). One patient experienced a G1 cytokine release syndrome (attributed to combination treatment). One death occurred on study due to septic shock that was not deemed to be treatment related. No patients discontinued therapy due to adverse events. Ultimately, this study conveyed that the combination therapy is safe and well tolerated at full dose.[91] The findings of this phase Ib trial support the initiation of the randomized phase III part of the study that aims to evaluate the efficacy and safety of the combination therapy compared to pembrolizumab alone (clinical trial number NCT 02263508). The combination will also be explored in an ongoing phase Ib/III multicenter, randomized open-label trial in patients with recurrent or metastatic squamous cell carcinoma of the head and neck (clinical trial number NCT02626000).

3.6 Pembrolizumab – a monoclonal antibody targeting PD-1

3.6.1 A brief overview of pembrolizumab

Pembrolizumab (previously named lambrolizumab and MK-3475), is a highly selective humanized monoclonal IgG4–kappa isotype antibody against PD-1 currently approved by the *Food and Drug Administration* (FDA) for the treatment of patients with advanced melanoma at a dose of 2mg/kg given every 3 weeks.[77-80]

3.6.2 Summary of clinical experience with pembrolizumab

The first dose-escalation phase 1 study involving patients with solid tumors showed that pembrolizumab was safe across 3 tested dose levels (1mk/kg; 3mg/kg and 10mg/kg) administered every 2 weeks; of note, the maximum tolerated dose was not reached and clinical responses were observed at all of the dose levels.[77] Subsequent studies confirmed the clinical activity of pembrolizumab. Hamid et al. initially investigated pembrolizumab at doses of 2mg/kg every 3 weeks and 10mg/kg given every 2 or 3 weeks in a melanoma-only

cohort in a non-randomized fashion in the KEYNOTE-001 trial.[78] Objective responses occurred in 38% of 135 included patients. Grade 3 or 4 adverse events occurred in only 13% of the patients. In a subsequent cohort of the same KEYNOTE-001 phase I trial, [79] 173 patients with advanced melanoma were randomized to receive pembrolizumab at 2mg/kg every 3 weeks or 10mg/mg every 3 weeks. ORR was 26% at both doses after a median follow up of 8 months, with no difference in OS between different doses (estimated OS at 1 year 58% vs 63%, 95% CI 0.68-1.75). In the expansion cohort of the same trial including a total of 411 patients, pembrolizumab resulted in objective responses in 40% untreated patients.[80]

3.7 Identifying predictive biomarkers for response to immunotherapy

One major challenge to harnessing immune checkpoint inhibitors in sarcomas is identifying patients who have the highest chance of benefiting from this modality of therapy. To address this question, lessons can be extrapolated from other tumor types and applied to sarcomas. We believe the heterogeneity inherent to sarcomas makes them an ideal group of tumors to validate a prospective biomarker for response to immune activating agents.

It is unclear how best to predict which patients will benefit from immune checkpoint inhibitors. While the initial phase I trial of nivolumab suggested tumors expressing PD-L1 by immunohistochemistry (IHC) may benefit more frequently from PD-1 blockade,[75] more recent data from the combination ipilimumab plus nivolumab trial has cast doubt on the theory that PD-L1 expression is necessary for therapeutic benefit. Among patients that received combination therapy, responses were seen both in patients with PD-L1 expression (6/13) or those without PD-L1 expression (9/22.)

At the ASCO 2014 meeting, there were data presented in multiple malignancies demonstrating benefit to PD-1/PD-L1 blockade for patients regardless of their PD-L1 expression. It is known that PD-L1 expression remains a dynamic marker that can change over time and under different conditions in the microenvironment. Tumor heterogeneity can also contribute to varied PD-L1 expression.[81] These data suggest that PD-L1 expression may change as a result of therapy with immune checkpoint inhibitors or that other mechanisms underlie the response to immune checkpoint blockade. There remains the need to define a better biomarker predictive of response to PD-1 blockade.

3.7.1 Tumor Neoantigens May Underlie Response to Immune Checkpoint Inhibition

Recently, a report by van Rooij et al associated a response to ipilimumab in a patient with melanoma with T cell recognition of a tumor-specific mutant protein, termed a ‘neoantigen’.[82] To do this, they performed whole exome sequencing of the melanoma tumor tissue and tumor infiltrating lymphocytes (TILs) and identified >1000 tumor-specific mutations. They then utilized NetMHC, an online predictor of Class I major histocompatibility complex (MHC)-specific affinities for specific sequences of 9-11 amino acids, to narrow the mutant sequences to 448 peptides predicted to bind with medium to high affinity to the patient’s CD8+ T cells.[83] These peptides were screened for binding with patient TILs, and they identified 3.3% of all patient CD8+ T cells reacted with a specific mutated epitope in the ataxia-telangiectasia and Rad3-related protein (ATR) pathway, suggesting this resulted in the clinical benefit seen in this patient.

Further support for neoantigen-specific immune surveillance has come from in vivo models of sarcoma. In a murine model of chemically-induced sarcomas arising in immune-deficient *Rag2*$^{-/-}$ mice, Matsushita et al reported that implantation into an immunocompetent murine

host resulted in “immune editing” of the tumor, and tumors with a greater neoantigen load were frequently rejected by the new host.[84] Similar results were seen in a conditional Kras-p53 knockout mouse model. Whereas the work of van Rooij et al and Matsushita et al suggests that certain key mutations predict response, DuPage et al and other authors imply that a higher overall mutational load and resulting neoantigen burden may lead to efficacy.[85] The Chan lab at MSKCC has proprietary data supporting the association between this patient-specific neoantigen analysis in melanoma with individual clinical benefit from ipilimumab and tremelimumab. Whole exome sequencing was performed on tumor tissue and matched blood samples from 64 patients with melanoma who were treated with anti-CTLA-4 blockade (ipilimumab or tremelimumab). A neoantigen signature incorporating both mutational load and patient-specific neoantigens was shown to separate patients with prolonged clinical benefit from patients with progressive disease. They then validated this signature in another set of 39 patients with melanoma who were treated with anti-CTLA-4 antibodies. In this validation set predicted neoantigens activated T cells from patients treated with ipilimumab. This work defines a genetic basis for benefit to anti-CTLA-4 blockade in melanoma and provides strong rationale for examining exomes of patients receiving other immunotherapies to similarly see if a genetic basis can be defined for response or resistance to these immunotherapies.[96]

Sarcoma is an ideal tumor subtype in which to test this hypothesis prospectively. The Singer laboratory at MSKCC has shown that different histologies show markedly different amounts of genetic alteration.[86] It is perhaps not surprising that a previous pilot study of ipilimumab in synovial sarcomas, a translocation-positive, genetically “simpler” tumor, produced no clinical responses.[87] There are currently no published whole exome mutation studies in sarcoma, which underscores how important this research will be to the sarcoma community.

3.8 Summary statement

Hence, there is strong rationale supporting the concept that, besides the antineoplastic effects of direct oncolysis, immune stimulation induced by GM-CSF and increased local antigen release induced by the oncolytic immunotherapy talimogene laherparepvec combined with immune checkpoint blockade using the anti-PD1 agent pembrolizumab could result in synergistic antitumoral antigen-specific activity in patients with metastatic and/or locally advanced sarcomas. The safety of this combination therapy has been explored in a phase Ib study in the setting of patients with treatment naïve, unresectable stage IIIB/IV melanoma. Ultimately, this study conveyed that the combination therapy is safe and well tolerated at full dose.[91] Therefore, it is reasonable to now explore the efficacy of this combination therapy in a phase II study in patients with advanced/metastatic sarcoma.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is a single-center, single-arm phase II clinical trial with additional cohorts to evaluate efficacy, as assessed by response rate, of the oncolytic herpes virus talimogene laherparepvec given in combination with the anti-PD1 monoclonal antibody pembrolizumab for patients with metastatic and/or locally advanced sarcomas.

Patients will initiate treatment with talimogene laherparepvec given intralesionally and pembrolizumab. Talimogene laherparepvec treatment will be given at Day 1 Week 1, and every 3 weeks thereafter. (Table 1). Pembrolizumab will be given at Day 1 week 1 and every

3 weeks thereafter (Table 1). Patients will be reassessed at week 8 and every 8 weeks thereafter.

Patients will be evaluated radiographically at baseline, week 8 (+/- 7 days) and every 8 weeks (+/- 7 days) subsequently until week 56 and then every 12 weeks thereafter or as per the discretion of the treating investigator. Response will be assessed using RECIST v1.1 (primary response assessment) and immune-related response criteria (irRECIST) (secondary response assessment).

The study will be sequentially monitored for pre-defined treatment-related toxicity events based on an early stopping rule as detailed in section 11. All study participants where feasible will undergo mandatory tumor biopsies, at baseline and week 8, of a distant site of disease. A site not intended to be injected is preferred for biopsy where feasible. Optional biopsies at progression will be offered. Serial blood samples will be obtained at baseline, during, and after treatment. Talimogene laherparepvec and pembrolizumab dosing should continue provided that the subject has no evidence of confirmed PD within 8 weeks of initial PD per RECIST, has no clear clinical deterioration and is able to tolerate the treatment. Treatment beyond progression will be allowed as long as patient is clinically benefitting, is tolerating the drug well and continues to meet all study treatment criteria.

Subjects with a CR or complete disappearance of the injectable lesion may stop intralesional injections of talimogene laherparepvec, but treatment with pembrolizumab will be continued for a maximum of 35 cycles of study therapy, unless one of the criteria for treatment discontinuation is met. Therapy will be discontinued due to confirmed progression of disease or clinical progression, disappearance of injectable lesions (talimogene laherparepvec only), intercurrent illness that prevents further administration of treatment, intolerance of study treatment or 24 months of treatment. Patients who discontinue study therapy after a maximum of 35 cycles of study therapy will be allowed to resume study therapy for an additional 17 cycles in the setting of progression of disease off study therapySafety data will be collected for up to 30 days following the last dose of the study drugs.

Study personnel will attempt to collect survival status for all patients who have confirmed disease progression after the end-of-study visit every 12 weeks (± 14 days) via telephone, email, or another method for up to 12 months after the end of treatment.

Patients who complete the study with a PR or CR per RECIST criteria will be followed every 12 weeks (± 14 days) until confirmed disease progression with the following assessments:

- Standard imaging including CT chest (with or without contrast), CT abdomen/pelvis (with contrast where renal function permits) and/or MRI abdomen/pelvis (with and without contrast) in addition to imaging of the affected area if deemed necessary by the study investigator
- Routine laboratory tests including CBC with differential, comprehensive serum chemistry panel (including glucose, blood urea nitrogen, creatinine, sodium, potassium, chloride, bicarbonate, calcium, total protein, albumin, serum bilirubin, alkaline phosphatase, ALT, and AST) and TSH
- MD visit (physical examination)

Following enrolment of the first 20 patients on this study additional cohorts will open. In the initial 20 patients enrolled on this study, the ORR overall was 35% and the ORR at 24 weeks was 30%. Objective response was observed in 5 histological subtypes including UPS, myxofibrosarcoma, cutaneous angiosarcoma, epithelioid sarcoma and undifferentiated sarcoma not otherwise specified. The additional cohorts will include a total of 40 patients and will be divided into 4 cohorts. Thirty patients with inoperable, locally advanced/metastatic sarcoma will be enrolled onto one of 3 cohorts based on sarcoma-specific subtype [i) UPS/myxofibrosarcoma, ii) epithelioid sarcoma, iii) cutaneous angiosarcoma]. Each cohort will enroll 10 patients. Patients with inoperable, locally advanced/metastatic sarcoma will be treated following the study design as highlighted above.

In the metastatic/locally advanced cohort, patients who achieve a CR or complete disappearance of the injectable lesion may stop intralesional injections of talimogene laherparepvec, but treatment with pembrolizumab will be continued. Study therapy may continue for a total of 35 cycles in the absence of confirmed progression of disease or clinical progression, disappearance of injectable lesions (talimogene laherparepvec only), intercurrent illness that prevents further administration of treatment, or intolerance of study treatment. Patients who discontinue study therapy after a maximum of 35 cycles of study therapy will be allowed to resume study therapy for an additional 17 cycles in the setting of progression of disease off study therapy. In the neoadjuvant setting, TVEC and pembrolizumab will continue for up to 8 cycles prior to surgical resection. On completion of surgery pembrolizumab alone will continue as tolerated for a total of 17 cycles (neoadjuvant and adjuvant therapy). Safety data will be collected for up to 30 days following surgical resection.

4.2 Intervention

Patients will be treated with intralesional injections of talimogene laherparepvec on Week 1 and every three weeks thereafter and intravenous pembrolizumab on Week 1 and every three weeks thereafter, for up to 35 cycles. Patients who discontinue study therapy after a maximum of 35 cycles of study therapy will be allowed to resume study therapy in the setting of progression of disease off study therapy.In the additional neoadjuvant cohort, patients will receive up to 8 cycles of study therapy beginning on Week 1. On completion of surgery, pembrolizumab alone will continue as tolerated for a total of 17 cycles (neoadjuvant and adjuvant therapy).
Talimogene laherparepvec will be administered intralesionally into injectable cutaneous, subcutaneous, accessible superficial or deep soft tissue and nodal lesions with or without ultrasound guidance. Talimogene laherparepvec must not be administered into visceral organ metastases. The initial dose of talimogene laherparepvec is up to 4.0 mL of 10^6 plaque-forming units (PFU)/mL on Week 1. Subsequent doses of talimogene laherparepvec are up to 4.0 mL of 10^8 PFU/mL on Week 4 and subsequent doses thereafter. When talimogene laherparepvec and pembrolizumab are administered on the same day, talimogene laherparepvec will be administered first.

Pembrolizumab at a dose of 200mg/dose will be administered intravenously at Week 1 and every 3 weeks (±3 days) thereafter. Pembrolizumab infusion should be administered in 30 minutes, with a window of -5 and +10 minutes, using an infusion pump.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1. Talimogene laherpevec (T-VEC)

5.1.1 Mechanism of action

Talimogene laherparepvec 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 talimogene laherparepvec replication in tumor tissue; normal cells are able to protect against talimogene laherparepvec 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.

5.1.2 Preclinical experience with talimogene laherparepvec

Talimogene laherparepvec 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. Nonclinical evaluation has also confirmed that GM-CSF enhances the immune response generated; enhancing both injected and uninjected tumor responses.

5.1.2.1 Preclinical pharmacology – talimogene laherparepvec

Nonclinical pharmacology studies, including in vitro studies of cytopathic effects and in vivo studies of efficacy in numerous tumor types, have been conducted with talimogene laherparepvec and its murine analog, OncoVEXmouseGM-CSF. Talimogene laherparepvec lyses a variety of in vitro human tumor cell lines in culture including colorectal cancer (HT29), breast cancer (MDA-MB-231), glioblastoma astrocytoma (U-87 MG), prostate adenocarcinoma (LNCaP), and malignant melanoma (SK-MEL-28) tested at a multiplicity of infection (MOI) between 0.1 and 5; essentially all tumor cells were killed less than 48 hours following infection in vitro. Talimogene laherparepvec affects not only the tumors into which it is injected, but also distant non-injected tumors, demonstrating a systemic beneficial effect from local administration. Talimogene laherparepvec suppresses tumor recurrence upon re-challenge with the same tumor type, and remains effective when animals have undergone previous exposure to wild-type HSV or are immunosuppressed with cyclosporin. Talimogene laherparepvec has been tested to evaluate the combined effects of either radiation or chemotherapy in preclinical studies. Both combinations were tolerated could support potential clinical studies with these other agents for the treatment of cancer.

5.1.2.2 Preclinical safety pharmacology and toxicology – talimogene laherparepvec

Toxicology – Talimogene laherparepvec

The toxicology program evaluated the safety of talimogene laherparepvec in a number of preclinical animal models. These pivotal single- and repeat-dose toxicology and embryo-fetal development studies were performed in accordance with Good Laboratory Practice (GLP) regulations, and Office of Economic Cooperation and Development standards. High and multiple doses of talimogene laherparepvec, up to 10^7 PFU/animal, were well tolerated in

immune competent mice following SC, IV, or intralesional injection. Key findings following repeated SC administration of talimogene laherparepvec included reversible inflammation at the injection site; increased total white blood cells, neutrophils and lymphocytes (all reversible); and evidence of transient immune activation (enlargement and increased germinal centers in the spleen, lymphoid hyperplasia in spleen and bone marrow). These effects are consistent with the normal response of animals to administration of a virus, and development of normal anti-viral immunity. As a general rule, mice treated with talimogene laherparepvec tended to seroconvert and develop anti-HSV-1 antibodies. No evidence of overt toxicity to any cell type or organ, and no evidence of virally-associated neuropathology/neurovirulence were observed in animals treated with talimogene laherparepvec. Intravenous injection of talimogene laherparepvec at doses of 10^5, 10^6, or 10^7 PFU/dose on gestation days 6, 9, 12, and 15 had no impact on embryo-fetal viability and development, or skeletal variations or malformations as assessed on gestation day 18. Assessment of maternal blood demonstrated a dose-dependent increase in viral DNA concentration. Systemic infection and lethality in nude mice treated with talimogene laherparepvec was observed at doses that are 10- to 100-fold higher than those that result in 100% lethality in nude mice treated with wild-type HSV-1, indicating that talimogene laherparepvec is attenuated for causing systemic infection. These data indicate an important role of host defenses, including both T and B cell function, in the immune response to talimogene laherparepvec and HSV-1 viruses. Talimogene laherparepvec was also shown in preclinical studies to be sensitive to anti-viral therapy. For additional information, refer to the talimogene laherparepvec Investigator's Brochure.

Biodistribution – talimogene laherparepvec

The biodistribution of talimogene laherparepvec in blood and all other tissues was evaluated using a validated quantitative polymerase chain reaction (qPCR) assay conducted in naïve or tumor-bearing BALB/c mice.

The biodistribution of talimogene laherparepvec was predominantly restricted to tumor, blood, and tissues likely associated with immune-mediated viral clearance (i.e., spleen, lymph node, liver). Overall, the available data align with results previously reported in other biodistribution studies. For additional information, refer to the talimogene laherparepvec Investigator's Brochure.

5.1.3 Summary of clinical experience with talimogene laherparepvec

Talimogene laherparepvec is approved in multiple regions and countries for the treatment of unresectable melanoma that is regionally or distantly metastatic.

Analyses of efficacy have been conducted for studies with talimogene laherparepvec administered as monotherapy for various tumors (001/01, 002/03, 002/03-E, 005/04, 005/05, and 005/05-E) and for studies of talimogene laherparepvec administered as combination therapy for various tumors (004/04, 006/09, 20110264, 20110265, and 20130232). Key results are briefly summarized below and further details can be found in the investigator brochure for talimogene laherparepvec :

Talimogene laherparepvec demonstrated initial biological activity as monotherapy (doses as low as 106 PFU/mL) in subjects with advanced solid tumors with

metastases in the skin or SC tissue as evidenced by necrosis or apoptosis in tumor biopsies (Study 001/01).

Talimogene laherparepvec resulted in an improvement in durable response rate (DRR), a primary endpoint of Study 005/05 (defined as complete response [CR] or partial response maintained for 6 months continuously and which had its onset on the first 12 months of treatment) compared with GM-CSF. At the primary analysis of overall survival (OS), a secondary endpoint of Study 005/05, median OS was 23.3 (95% CI: 19.5, 29.6) months in the talimogene laherparepvec 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 compared with GM-CSF (23.3 months, 95% CI: 19.5 to 29.6 vs 18.9 months, 95% CI: 16.0, 23.7; 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 for the treatment of melanoma.
The high proportion of tumors that decreased in size and high rate of histopathological response at surgery suggested clinical activity with talimogene laherparepvec in combination with cisplatin and radiation in subjects with SCCHN (Study 004/04). Further investigations in a larger sample set were planned in the phase 3 study (006/09); however, this phase 3 study was terminated in July 2011 in light of emerging evidence regarding the influence of human papillomavirus status and smoking on prognosis following chemoradiation, and effects of these factors on the likelihood of study success.
In the phase 2 portion of Study 20110264, a phase 1b/2 study evaluating the combination of talimogene laherparepvec and ipilimumab, treatment with talimogene laherparepvec and ipilimumab resulted in a statistically significant improvement in the primary endpoint of ORR (as evaluated by the investigator using modified immune-related response criteria [irRC]) compared with ipilimumab (38.8% vs 18.0%; unadjusted odds ratio 2.9, 95% CI: 1.5, 5.5; p-value = 0.002). Median progression-free survival (PFS) time was 8.2 months in the talimogene laherparepvec and ipilimumab group and 6.4 months in the ipilimumab group (HR 0.83, 95% CI: 0.56, 1.23; p = 0.348).
In the phase 1b portion of Study 20110265, a phase 1b/3 study evaluating the combination of talimogene laherparepvec and pembrolizumab (Long et al, 2016), 21 subjects received talimogene laherparepvec and pembrolizumab in combination. At the time of the primary analysis, the confirmed ORR and complete response rate were 57.1% and 23.8%, respectively, per irRC. The unconfirmed objective response rate and complete response rate were 66.7% and 28.6%, respectively. Median PFS was not reached, with 71% of subjects progression free at 6 months. Further follow-up is ongoing.
In the phase 1b portion of Study 20130232, a phase 1b/3 study evaluating the combination of talimogene laherparepvec and pembrolizumab in subjects with HNSCC, 36 subjects received talimogene laherparepvec and pembrolizumab in combination. The unconfirmed objective response rate was 15.6% (95% CI: 5.3, 32.8) and the confirmed objective response rate was 9.4% (95% CI: 2.0, 25.0), per irRC.

Pharmacodynamics and Pharmacokinetics of talimogene laherparepvec in Humans

Five clinical studies were conducted to characterize the dosing regimen, kinetics, viral shedding, clearance, anti-HSV-1 serostatus, and GM-CSF expression in tumor tissue of talimogene laherparepvec in subjects with metastatic melanoma and other cancer types including the first-in-human study[92] and 4 other studies primarily designed to evaluate efficacy and safety but provided supportive data (clinical trial number NCT02574260, phase I/II study in SCCHN[93], a phase II study in melanoma[50] and a phase III study in melanoma.[49] Of these 4 studies, 2 evaluated subjects with metastatic melanoma (and 005/05).[50,49,] The other 2 studies evaluated subjects in other indications (pancreatic cancer, clinical trial number NCT 00402025,and cancer of the head and neck).[93]

Clinical Biodistribution and Shedding Results – talimogene laherparepvec

Data from the assessment of viral biodistribution of talimogene laherparepvec in humans are available from a number of clinical studies.[92, 93, 50] All biodistribution data were based on qPCR and not viral culture; therefore, the potential for infectivity was not evaluable by this method. In summary, the biodistribution pattern of talimogene laherparepvec in blood and urine demonstrated consistently across studies that low copy numbers of viral DNA were sporadically detected in blood samples from 33% of subjects and urine samples from 22% of subjects from 1 hour to 1 week after intralesional injection. Blood and urine samples were negative by 2 weeks post-injection in those subjects for whom additional samples were available. The copy numbers of virus detected in blood and urine in all subjects at all collection time points was far lower than those present in the doses administered during treatment.

Viral shedding was assessed by the collection of swab samples from the surface of injected tumors and the exterior dressing. The samples were analyzed by a plaque assay or 50% tissue culture infective dose (TCID50; Study 20120324 only) to determine if any infectious virus was present and to assess whether the occlusive dressings provided adequate containment for virus present at the tumor surface. The infectivity assays did not distinguish between wild-type HSV-1 and talimogene laherparepvec. It was assumed that a positive assay result indicated the presence of talimogene laherparepvec since the probability that wild-type HSV-1 was present on the surface of injected tumors and/or dressings would be very low.
Investigative swab samples were collected after each injection in Studies 001/01 and 004/04 and after the first injection in Study 002/03. In all studies (with the exception of pancreatic cancer Study 005/04), “reactive” swabs were collected from herpes labialis or other non-injected lesions that arose during treatment and that were suspected to be herpetic in origin, and from injected tumors that were oozing or weeping.
The most comprehensive set of samples (ie, in terms of the number of time points tested) was obtained from Study 001/01. Overall, at any time point, a low percentage of subjects (13% [4 of 30]) had swabs that were positive for virus at the tumor site. These samples were further tested by a specific custom polymerase chain reaction (PCR) assay to distinguish between talimogene laherparepvec and wild-type HSV; it was determined that the virus detected in 3 of the swab samples was talimogene laherparepvec and not wild-type HSV.
Results from Studies 002/03 and 004/04 were consistent with those from Study 001/01. Investigative swabs collected from the first 28 subjects in Study 002/03 (before the

protocol amendment removed this testing) showed that only a single subject (4%) had a positive investigative swab sample from the tumor site and 3/17 subjects (18%) in Study 004/04 had investigative swabs that were positive at the tumor site. Combined with results from Study 001/01, viral shedding was observed in 11% of subjects across the 3 studies. The longest time that infectious virus was detected in these injection site swabs was 2 weeks post-injection.

All swabs of the exterior of the dressing were negative at all time points tested across all studies. Thus, it appeared that the dressings were used effectively and prevented shedding of any virus from the tumors into the environment.

In Study 005/05, 18 “reactive” swabs from oozing or weeping lesions as described earlier were collected from 12 subjects. Of these 18 swabs, 11 were collected from a tumor that had been previously injected with talimogene laherparepvec, 4 were collected from non-injected melanoma lesions, and 3 were collected from other sites or an unknown site. None of the 18 samples tested positive for infectious HSV (ie, talimogene laherparepvec or wild-type) using the plaque assay.

In first-in-human study (001/01), staining of tumor biopsies with anti-HSV antibody indicated that talimogene laherparepvec antigens co-located with tumor necrosis. In the phase1/2 study of talimogene laherparepvec in the treatment of subjects with locally advanced SCCHN (004/04), needle biopsy tumor tissue samples were obtained for qPCR analysis from injected and neighboring uninjected neck nodes in 16 subjects prior to neck dissection. Detection of viral DNA was observed in the injected tumors of 7 subjects and in the uninjected tumors of 1 subject. Additional biodistribution and shedding data were collected in Study 20120324. The

final analysis of this phase 2, multicenter, single-arm study to investigate the biodistribution and shedding of talimogene laherparepvec in 50 subjects with unresected, stage IIIB to IVM1c melanoma has been conducted. Blood and urine samples were collected in addition to swabs from the surface of injected lesions, exterior of occlusive dressings, oral mucosa, anogenital regions, and lesions of suspected herpetic origin to test for the presence of talimogene laherparepvec DNA by qPCR test. In addition, swabs with detectable talimogene laherparepvec DNA were tested for the presence of infective virus by the TCID50 assay.

Talimogene laherparepvec DNA was detected with the lowest frequency in samples from the oral mucosa (1% of samples in 13% of subjects), the anogenital area (2% of samples in 19% of subjects, with almost all detected at a concentration below the lower limit of quantification of the assay), and from urine (3% of samples in 32% of subjects). In contrast, and consistent with the method of administration, talimogene laherparepvec DNA was detected with the greatest frequency in swabs of injected lesions (49% of samples in 100% of subjects) and in blood (35% of samples in 98% of subjects). Most of the positive samples were obtained during cycle 2 when talimogene laherparepvec was administered at a concentration of 108 PFU/mL for the first time.

Among the swabs of the surface of injected lesions, the incidence of viral infectivity via TCID50 assay was low (8/740 samples [1%]). Seven of these samples were from cycle 1, and 1 positive sample was from cycle 2; no swabs tested positive for viral activity by TCID50 testing after cycle 2. Live virus was never detected among 1085 swabs of the exterior of occlusive dressings. Of 37 swabs from lesions of suspected herpetic origin taken from 19 subjects, 4 swabs from 3 subjects had detectable talimogene laherparepvec DNA, but all were negative for viral infectivity by TCID50 assay.

For additional information, refer to the talimogene laherparepvec Investigator's Brochure.

Human GM-CSF Expression – talimogene laherparepvec

Human GM-CSF expression was measurable in the fine needle aspirates of injected tumors in 11 of the 13 samples tested in the first-in-human study during the single-dose phase.[92] The level of human GM-CSF expression was dependent on the dose of talimogene laherparepvec. Higher levels of GM-CF were expressed in seronegative subjects than in seropositive subjects. Human GM-CSF levels in serum samples, as assessed by enzyme-linked immunosorbent assay (ELISA), were below the limit of detection of the assay at all time points tested. For additional information, refer to the talimogene laherparepvec Investigator's Brochure.

Immune Response in Clinical Studies – talimogene laherparepvec

For initial serostatus testing, 69% of all subjects entering talimogene laherparepvec clinical studies were positive for the HSV-1 antibody. For the follow-up serostatus testing, all previous seronegative subjects converted to seropositive status, a 100% conversion rate. HSV-1 serostatus was determined using indirect ELISA for HSV-1 antibody status. For most subjects, seroconversion occurred during the 3 weeks after the first injection of talimogene laherparepvec. After the second injection of talimogene laherparepvec all subjects experienced seroconversion.[92, 93, 50] No difference in efficacy or safety was seen between subjects who were seropositive for HSV-1 versus those who were seronegative for HSV-1 at baseline. For additional information, refer to the talimogene laherparepvec Investigator's Brochure.

Efficacy of Talimogene Laherparepvec in Humans – talimogene laherparepvec

Analyses of efficacy have been conducted for 4 studies[92, 49, 50] with talimogene laherparepvec as monotherapy for various tumors and for 2 studies with talimogene laherparepvec as combination therapy for head and neck cancers (clinical trial number NCT01161498).[93] these are briefly summarized below:

- Talimogene laherparepvec demonstrated initial biological activity as monotherapy (doses as low as 10^6 PFU/mL) in subjects with advanced solid tumors with metastases in the skin or SC tissue as evidenced by necrosis or apoptosis in tumor biopsies .[92]

- Talimogene laherparepvec resulted in an improvement in durable response rate (DRR), a primary endpoint of the phase III study investigating the efficacy of talimogene laherparepvec in patients with unresectable advanced melanoma(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) compared with GM-CSF.[49] At the primary analysis of overall survival (OS), a secondary endpoint of this study , median OS was 23.3 (95% CI: 19.5, 29.6) months in the talimogene laherparepvec arm and 18.9 (95% CI: 16.0, 23.7) months in the GM-CSF arm (HR 0.79; 95% CI: 0.62,

1.00; p = 0.051). Results from the phase 2 study in melanoma also support the efficacy of talimogene laherparepvec for the treatment of melanoma.[50]

• The high proportion of tumors that decreased in size and high rate of histopathological response at surgery suggested clinical activity with talimogene laherparepvec in combination with cisplatin and radiation in subjects with SCCHN .[94] Further investigations in a larger sample set were planned in the phase 3 study (clinical trial number NCT01161498); however, this phase 3 study was terminated in July 2011 in light of emerging evidence regarding the influence of human papillomavirus status and smoking on prognosis following chemoradiation, and effects of these factors on the likelihood of study success.

Safety of Talimogene Laherparepvec in Humans – talimogene laherparepvec

At the time of the study-specific data cutoff dates, 486 subjects have received talimogene laherparepvec (with doses from 10^4 to 10^8 PFU/mL) across 15 studies.

Overall, most adverse events reported in subjects administered talimogene laherparepvec are non-serious and primarily include flu-like symptoms and injection site reactions. Most fatal adverse events reported in subjects administered talimogene laherparepvec were reported in the setting of disease progression.

The most common side effects in the OPTiM study were chills (talimogene laherparepvec, 49%; GM-CSF, 9%), pyrexia (43%; 9%), injection-site pain (28%; 6%), nausea (36%; 20%), influenza-like illness (30%; 15%), and fatigue (50%; 36%).Grade ≥ 3 adverse events occurred in 36% of subjects receiving talimogene laherparepvec and 21% of subjects receiving GM-CSF. The only grade 3/4 adverse events occurring in ≥ 5 subjects was cellulitis (talimogene laherparepvec, n=6 [2.1%];
GM-CSF, n=1 [<1%]). Of 10 fatal adverse events in the talimogene laherparepvec arm, eight were attributable to disease progression. The remaining two fatal adverse events (sepsis in the setting of salmonella infection; myocardial infarction) were not considered treatment-related per investigator.[49]
Additional identified risks, potential risks and adverse drug reactions associated to talimogene laherparepvec are described in detail in section 11.2.

5.1.4 Formulation, Storage and Packaging – talimogene laherparepvec

Talimogene laherparepvec will be manufactured by Amgen
Talimogene laherparepvec will be presented as a sterile frozen liquid in a single-use 2.0cc Crystal Zenith vial with a gray Fluorotec®-coated chlorobutyl elastomer stopper, aluminum seal, and polypropylene cap. Each vial contains a minimum of 1.0 mL talimogene laherparepvec at either 10^6 PFU/mL or 10^8 PFU/mL concentrations. The supply for the 10^6 PFU/mL concentration will be packaged separately from the supply for the 10^8 PFU/mL concentration.
Talimogene Laherparepvec will be stored, prepared and handled as per Amgen's Pharmacy Information guide and local institutional guidelines.

Please refer to the Pharmacy Information Guide and local institutional guidelines for additional information regarding the formulation and packaging of talimogene laherparepvec.

5.1.5 Preparation and administration of talimogene laherparepvec

Preparation of Talimogene Laherparepvec:

- Amgen's pharmacy information guide and Local institutional guidelines will be followed with regards to the preparation of talimogene laherparepvec

Administration:
Talimogene laherparepvec must be prepared and administered by a qualified healthcare professional.

The total volume of talimogene laherparepvec to be prepared will be based on investigator evaluation of injectable lesions and estimation of the total volume needed based on the talimogene laherparepvec Injection Volume Guideline Based on Tumor Size Table 3 (detailed information described in Pharmacy Information Guide). Prescribe the estimated total volume by rounding up to the nearest 1.0 mL.
The maximum volume of talimogene laherparepvec administered at any dose is 4.0 mL for any individual lesion. The maximum dose in any one treatment is 4.0 mL. Use the maximum amount whenever lesions allow.

Table 3. Talimogene laherparepvec Injection Volume Guideline Based on Tumor Size*

Tumor Size (longest dimension)	Maximum Injection Volume
> 5.0 cm	4.0 mL
> 2.5 cm to 5.0 cm	2.0 mL
> 1.5 cm to 2.5 cm	1.0 mL
> 0.5 cm to 1.5 cm	0.5 mL
≤ 0.5 cm	0.1 mL

Talimogene laherparepvec should be injected into viable tissue if available and direct injection into necrotic tumor tissue should be avoided.

- Personal protective equipment (PPE) as per the local institutional guidelines for talimogene laherparepvec is required during preparation and administration.

Drug Administration: Administer by intralesional injection into cutaneous, subcutaneous, and/or nodal lesions that are visible, palpable, or detectable by ultrasound

First dose: Inject up to 4 mL at a concentration of 10^6 (1 million) PFU/mL. Where clinically appropriate and feasible inject largest lesion(s) first; where feasible inject remaining lesion(s) based on lesion size until maximum injection volume is reached or all lesions have been treated.

Second dose and all subsequent doses (every three weeks after first dose): Inject up to 4 mL at a concentration of 10^8 (100 million) PFU/mL. All reasonably injectable lesions (cutaneous, subcutaneous and nodal disease that can be injected with or without ultrasound [US] 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 where clinically appropriate and feasible:

- 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 guidelines of the algorithm in Table 3, and the prioritization model 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 (4.0 mL) has been reached or there are no further injectable lesions, whichever comes first.

Manufacturer's and Local institutional guidelines for the preparation and administration of talimogene laherparepvec and the management of talimogene laherparepvec contaminated materials or surfaces will be followed.

5.2 Pembrolizumab

Information extracted from Pembrolizumab Prescribing Information, available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125514lbl.pdf

5.2.1 Mechanism of action - Pembrolizumab

Pembrolizumab (formerly known as MK-3475 or lambrolizumab), is a highly selective humanized monoclonal IgG4–kappa isotype antibody against PD-1, that acts by blocking its interaction with PD-L1 and PD-L2. Pembrolizumab is currently approved by the FDA for the treatment of patients with advanced melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T cell proliferation and cytokine production. Upregulation of PD-1 ligands occur in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.

The theoretical molecular weights of the heavy and light chains derived from the amino acid sequences, excluding glycosylation, are 49.4 kDa and 23.7 kDa, respectively. The antibody is heterogeneously glycosylated at asparagine 297 within the Fc domain of each heavy chain, yielding molecular weights typically ranging between 148.9 and 149.5 kDa, depending on the attached glycan chains.

5.2.1 Non-clinical pharmacology - Pembrolizumab

Pembrolizumab is a potent and highly selective humanized mAb designed to block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab potently blocks binding to both ligands with half maximal inhibitory concentration (IC50) values below1 nM. Pembrolizumab enhances T cell responses in human donor blood cell cultures with an EC50 of ~0.1 to 0.3 nM. Pembrolizumab binds to cynomologus PD-1 with similar affinity, blocking

activity, and demonstrates equivalent enhancement of cynomologus T cell responses. It does not cross-react with rodent PD-1.

Pembrolizumab strongly enhances T lymphocyte immune responses in cultured blood cells from healthy human donors, cancer patients, and primates. The antibody potentiates existing immune responses only in the presence of antigen-receptor stimulation and does not nonspecifically activate all T cells. Using an anti-mouse PD- 1 analog antibody, PD-1 blockade is demonstrated to significantly inhibit tumor growth in a variety of syngeneic murine tumor models. In experiments in mice, anti- PD-1 therapy is synergistic with chemotherapeutic agents, such as gemcitabine and 5-FU and this combination therapy results in increased efficacy, as well as complete regression rates *in vivo*.

The dissociation constants (KD) of pembrolizumab binding to human and cynomologus monkey PD-1 were determined by measurement of kinetic rate constants (on/off) in a solid phase format (ForteBiobiolayer-interferometry [BLI]). BLI measurements demonstrated that format (ForteBiobiolayer-interferometry [BLI]). BLI measurements demonstrated that pembrolizumab binds human PD-1 with a fast association rate, dissociates very slowly, and has a high affinity of 29 pM (Table 2). The ability of pembrolizumab to block the binding of PD-1 ligands, PD-L1 and PD-L2, to human or cynomologus monkey PD-1 was measured using a competitive binding assay and detection by fluorometric microvolume assay technology (FMAT). Pembrolizumab potently blocks binding to both PD-1 ligands with IC50 values below 1 nM.

5.2.2 Non-clinical toxicology - Pembrolizumab

Animal Toxicology and/or Pharmacology

In animal models, inhibition of PD-1 signaling resulted in an increased incidence of infections and enhanced inflammatory responses. M. tuberculosis-infected PD-1 knockout mice exhibit markedly decreased survival compared with wild-type controls, which correlated with increased bacterial proliferation and inflammatory responses in these animals. PD-1 knockout mice have also shown decreased survival following infection with lymphocytic choriomeningitis virus (LCMV). Administration of pembrolizumab in chimpanzees with naturally occurring chronic hepatitis B infection resulted in two out of four animals with significantly increased levels of serum ALT, AST, and GGT, which persisted for at least 1 month after discontinuation of pembrolizumab.

In the 1-month and 6-month toxicology study in cynomologus monkeys, pembrolizumab administered once a week and once every other week respectively, intravenously up to 200 mg/kg resulted in no adverse treatment related effects. The exposure multiple based on a predicted AUC 0-tau of 4464 µg.day/mL at the maximum anticipated human clinical dose of 10 mg/kg Q2W or Q3W is 15-fold at 200 mg/kg, the NOAEL for the 6-month monkey study. Additionally, in the tissue cross-reactivity study of pembrolizumab with human and monkey tissues demonstrated the expected on-target staining of the membranes of mononuclear leukocytes in both species. Off-target cross-reactivity staining was also noted in both species but was limited to cytoplasm of various cell types/tissues and the stroma (extracellular connective tissue matrix), and was considered related to the experimental method artifacts,

i.e. tissue processing for IHC, that are well recognized limitations of tissue cross-reactivity studies and, thus not considered toxicologically relevant.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No studies have been performed to test the potential of pembrolizumab for carcinogenicity or genotoxicity. Fertility studies have not been conducted with pembrolizumab. In 1-month and 6-month repeat-dose toxicology studies in monkeys, there were no notable effects in the male and female reproductive organs; however, most animals in these studies were not sexually mature.

5.2.3 Pharmacokinetics - Pembrolizumab

The pharmacokinetics of pembrolizumab was studied in 479 patients who received doses of 1 to 10 mg/kg every 2 weeks or 2 to 10 mg/kg every 3 weeks. Based on a population pharmacokinetic analysis, the mean [% coefficient of variation (CV%)] clearance (CL) is 0.22 L/day (28%) and the mean (CV%) elimination half-life (t1/2) is 26 days (24%). Steady-state concentrations of pembrolizumab were reached by 18 weeks of repeated dosing with an every 3-week regimen and the systemic accumulation was 2.1-fold. The peak concentration (Cmax), trough concentration (Cmin), and area under the plasma concentration versus time curve at steady state (AUCss) of pembrolizumab increased dose proportionally in the dose range of 2 to 10 mg/kg every 3 weeks.

Specific Populations: The effects of various covariates on the pharmacokinetics of pembrolizumab were assessed in population pharmacokinetic analyses. The CL of pembrolizumab increased with increasing body weight; the resulting exposure differences were adequately addressed by the administration of a weight-based dose. The following factors had no clinically important effect on the CL of pembrolizumab: age (range 18-94 years), gender, renal impairment, mild hepatic impairment, and tumor burden. The effect of race could not be assessed due to limited data available in non-White patients.

Renal Impairment: The effect of renal impairment on the CL of pembrolizumab was evaluated by population pharmacokinetic analyses in patients with mild (eGFR 60 to 89 mL/min/1.73 m2; n=210), moderate (eGFR 30 to 59 mL/min/1.73m2; n=43), or severe (eGFR 15 to 29 mL/min/1.73m2; n=2) renal
impairment compared to patients with normal (eGFR greater than or equal to 90 mL/min/1.73m2; n=221) renal function. No clinically important differences in the CL of pembrolizumab were found between patients with renal impairment and patients with normal renal function *[see Use in Specific Populations (8.6)].*

Hepatic Impairment: The effect of hepatic impairment on the CL of pembrolizumab was evaluated by population pharmacokinetic analyses in patients with mild hepatic impairment (TB less than or equal to ULN and AST greater than ULN or TB between 1 and 1.5 times ULN and any AST; n=59) compared to patients with normal hepatic function (TB and AST less than or equal to ULN; n=410). No clinically important differences in the CL of pembrolizumab were found between patients with mild hepatic impairment and normal hepatic function. KEYTRUDA has not been studied in patients with moderate (TB greater than 1.5 to 3 times ULN and any AST) or severe (TB greater than 3 times ULN and any AST) hepatic impairment *[see Use in Specific Populations (8.7)].*

5.2.4 Summary of clinical experience with pembrolizumab

The efficacy of pembrolizumab was investigated in a multicenter, open-label, randomized (1:1), dose-comparative, activity-estimating cohort. Key eligibility criteria were unresectable or metastatic melanoma with progression of disease; refractory to two or more doses of ipilimumab (3 mg/kg or higher) and, if BRAF V600 mutation-positive, a BRAF or MEK inhibitor; and disease progression within 24 weeks following the last dose of ipilimumab. The trial excluded patients with autoimmune disease; a medical condition that required immunosuppression; and a history of severe immune-mediated adverse reactions with ipilimumab, defined as any Grade 4 toxicity requiring treatment with corticosteroids or Grade 3 toxicity requiring corticosteroid treatment (greater than 10 mg/day prednisone or equivalent dose) for greater than 12 weeks. Patients were randomized to receive 2 mg/kg (n=89) or 10 mg/kg (n=84) of pembrolizumab every 3 weeks until unacceptable toxicity or disease progression that was symptomatic, was rapidly progressive, required urgent intervention, occurred with a decline in performance status, or was confirmed at 4 to 6 weeks with repeat imaging. Assessment of tumor status was performed every 12 weeks. The major efficacy outcome measures were confirmed overall response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1) as assessed by blinded independent central review and duration of response. Among the 173 patients enrolled, the median age was 61 years (36% age 65 or older); 60% male; 97% White; and 66% and 34% with an ECOG performance status 0 and 1, respectively. Disease characteristics were BRAF V600 mutation (17%), elevated lactate dehydrogenase (39%), M1c (82%), brain metastases (9%), and two or more prior therapies for advanced or metastatic disease (73%). The ORR was 24% (95% confidence interval: 15, 34) in the 2 mg/kg arm, consisting of 1 complete response and 20 partial responses. Among the 21 patients with an objective response, 3 (14%) had progression of disease 2.8, 2.9, and 8.2 months after initial response. The remaining 18 patients (86%) had ongoing responses with durations ranging from 1.4+ to 8.5+ months, which included 8 patients with ongoing responses of 6 months or longer. One additional patient developed two new asymptomatic lesions at the first tumor assessment concurrent with a 75% decrease in overall tumor burden; Pembrolizumab was continued and this reduction in tumor burden was durable for 5+ months. There were objective responses in patients with and without BRAF V600 mutation-positive melanoma. Similar ORR results were observed in the 10 mg/kg arm.

As of 18-Oct-2013, 1,000 patients have been treated with pembrolizumab at several dose-schedules, including 10 mg/kg every 2 weeks. Pembrolizumab has been generally well tolerated, as expected based on preclinical findings and other anti-PD- 1 monoclonal antibodies. As of 18-Oct-2013 no serious infusions reactions had been reported, however, since the potential exists in anti-PD-1 monoclonal antibodies, investigators should be vigilant to this possibility. There is no contraindication to further clinical investigation with pembrolizumab. Pharmacokinetics were as expected, based on pembrolizumab being an IgG mAb and based on preclinical data, which support dosing once every 2 or 3 weeks. Pembrolizumab monotherapy induces an ORR of 25%/27% in patients with ipilimumab-exposed melanoma by central independent RECIST and oncology review/investigator assessed irRECIST, respectively. Pembrolizumab monotherapy induces an ORR of 39%/43% in patients with ipilimumab-naive melanoma by central independent RECIST and oncology review/investigator assessed irRECIST, respectively. These responses are remarkably durable. The preliminary 1-year survival rate for patients, many of whom have had multiple therapies, including ipilimumab, who receive pembrolizumab is 81%. Pembrolizumab

monotherapy induces an ORR of 21%/24% in patients with previously-treated NSCLC by central independent RECIST/investigator assessed irRECIST, respectively, with these responses also remarkably durable. Preliminary data suggest higher levels of PD-L1 expression in tumors of NSCLC are associated with increased activity (ORR 67% by investigator assessed irRECIST/57% by central independent RECIST); additional data are required to define the optimal PD-L1 cut point. The most commonly reported treatment emergent AEs experienced are fatigue (43.8%), nausea (26.7%), cough (25.3%), pruritus (24.6%), diarrhea (22.3%) and rash (21.5%). Immune-related adverse events were reported in 21.4% of melanoma patients; most of these events (15.8%) were considered drug-related by the
investigator. The most commonly reported, immune-related adverse events across the dose-schedules are rash (3.2%), pruritus (2.9%), vitiligo (2.9%), hypothyroidism (2.7%), arthralgia (2.2%), diarrhea (2.2%), and pneumonitis (1.9%). Review of the overall benefit:risk ratio of pembrolizumab favors enrollment of eligible patients into clinical trials of pembrolizumab. The preliminary data suggest that a dose of pembrolizumab at 2 mg/kg Q3W is appropriate for patients with melanoma.

No formal pharmacokinetic drug interaction studies have been conducted with KEYTRUDA.

Additional identified risks, potential risks and adverse drug reactions associated to pembrolizumab are described in detail in section 11.3.

5.2.3 Formulation, Storage and Packaging - Pembrolizumab

Pembrolizumab will be manufactured by Merck.

Pembrolizumab is supplied as pembrolizumab 50 mg lyophilized powder in a single-use vial for reconstitution or as Pembrolizumab 100 mg/4ml Solution for Injection

Reconstituted and diluted solutions of pembrolizumab should be stored either:

- At room temperature for no more than 4 hours from the time of reconstitution. This includes room temperature storage of reconstituted vials, storage of the infusion solution in the IV bag, and the duration of infusion.
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of reconstitution. If refrigerated, allow the diluted solution to come to room temperature prior to administration.

Product should not be frozen.

5.2.4 Administration of pembrolizumab

Pembrolizumab must be prepared and administered by a qualified healthcare professional.

Pembrolizumab at a dose of 200 mg will be administered intravenously on Week 1 and every 3 weeks (±3 days) thereafter. When talimogene laherparepvec and pembrolizumab are administered on the same day, talimogene laherparepvec must be administered first.

Pembrolizumab infusion will be administered as a 30-minute intravenous infusion. Investigators should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+ 10 min). A central catheter is not required for infusion; however if a subject has a central venous catheter in place, it is recommended that it be used for the infusion. A 0.2 or 0.22 µm in-line filter made of polyethersulfone (PES) must be used during administration to remove any adventitious particles. If the infusion set does not contain a 0.2 or 0.22 µm in-line filter, it is recommended to use an extension line containing the filter.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

Describe the characteristics of the patient/subject population.

6.1 Subject Inclusion Criteria

Patients must fulfill all of the following criteria to be eligible for admission to the study:

- Male or female age ≥ 18 years at the time of informed consent.
- Be willing and able to provide written informed consent/assent for the trial.
- Be willing to comply with treatment protocol
- Subjects must have a histologically confirmed metastatic and/or locally advanced inoperable sarcoma (metastatic/locally advanced cohort)
- For histology specific additional metastatic cohorts, patients must have undifferentiated pleomorphic sarcoma/myxofibrosarcoma, epithelioid sarcoma or cutaneous angiosarcoma.
- Subjects must have at least 1 injectable cutaneous, subcutaneous (superficial or deep) soft tissue or nodal lesion ≥ 10 mm in longest diameter. Of note, bone lesions are not eligible for injection unless there is a soft tissue component that is amenable to injection. Injectable lesions must not be chosen from a previously irradiated field unless there has been radiographically and/or pathologically documented tumor progression in that lesion prior to enrollment. Subjects with locally advanced/metastatic sarcoma must have at least one prior line of systemic therapy (e.g. chemotherapy, immunotherapy, targeted or biological therapy) An exception to this criterion will be made for patients with sarcoma histological subtypes for which there is no known standard systemic therapy (e.g.,epithelioid sarcoma). Treatment naïve patients may be enrolled if they have refused standard systemic treatment. Prior adjuvant therapy will not count provided it was completed more than 6 months previously.
- Adequate performance status: ECOG 0 or 1/KPS 100-70%

- Adequate organ function determined within 3 weeks of treatment initiation, defined as follows:

  I. Hemoglobin ≥ 8.0 g/dl
  II. Absolute neutrophil count ≥ 1,000/mm^3 (1.0 x 10^9/L)
  III. Platelet count ≥ 75,000/mm^3 (75 x 10^9/L)
  IV. Serum bilirubin ≤ 1.5 x ULN OR direct bilirubin ≤ ULN for a subject with total bilirubin level > 1.5 x ULN

V. Aspartate aminotransferase (AST) ≤ 2.5 x ULN OR ≤ 5 x ULN for subjects with liver metastases
VI. Alanine aminotransferase (ALT) ≤ 2.5 x ULN OR ≤ 5 x ULN for subjects with liver metastases
VII. Alkaline Phosphatase < 5 x ULN
VIII. Albumin ≥2.5mg/dL
IX. Serum creatinine ≤ 1.5 x ULN or a measured or calculated[a] creatinine clearance ≥ 60mL/min for subject with creatinine levels > 1.5 x institutional ULN (Note: Creatinine clearance need not be determined if the baseline serum creatinine is within normal limits. GFR can also be used in place of creatinine or CrCl)
X. International Normalized Ratio (INR) or Prothrombin Time (PT) ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
XI. Activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN unless subject is receiving anticoagulant therapy as long as PT and PTT is within therapeutic range of intended use of anticoagulants

[a]Creatinine clearance should be calculated per institutional standard

- Female subject of childbearing potential should have a negative serum pregnancy testing at screening visit and within 72 hours prior to the first dose of study medication.

6.2 Subject Exclusion Criteria

Patients who fulfil any of the following criteria are not eligible for admission to the study:

- Uncontrolled intercurrent illness including active infection requiring systemic therapy or symptomatic congestive heart failure within 6 months
- Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

- Evidence of clinically significant immunosuppression such as the following:

    - Primary immunodeficiency state such as Severe Combined Immunodeficiency Disease
    - Concurrent opportunistic infection

  - Receiving systemic immunosuppressive therapy (> 2 weeks) including oral steroid doses > 10 mg/day of prednisone or equivalent within 7 days prior to enrollment. However, in the setting of non-immune mediated indications for use, chronic/active low dose steroid use may be permitted at the discretion of the principal investigator.

- Known history of human immunodeficiency virus (HIV) disease.
- History or evidence of symptomatic autoimmune disease (e.g., pneumonitis, glomerulonephritis, vasculitis, or other), or history of active autoimmune disease that has required systemic treatment (i.e., use of corticosteroids, immunosuppressive drugs or biological agents used for treatment of autoimmune diseases) in past 2 years prior to enrollment. 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.
- Active herpetic skin lesions or prior complications of herpetic infection
- Require intermittent or chronic treatment with an intravenous or oral antiherpetic drug (e.g., acyclovir), other than intermittent topical use
- Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).
- Received live vaccine or live-attenuated vaccine within 30 days prior to enrollment. Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.
- Has a known history of active TB (Bacillus Tuberculosis)
- Female subject is pregnant or breast-feeding, or planning to become pregnant or male subject is planning to father a child within the projected duration of the trial, starting with the pre-screening or screening visit, during study treatment and through 3 months after the last dose of talimogene laherparepvec or 4 months after the last dose of pembrolizumab, whichever is later.
- Male and female subjects of childbearing potential who are unwilling to use acceptable method(s) of effective contraception during study treatment and through 3 months after the last dose of talimogene laherparepvec and 4 months after the last dose of pembrolizumab. (Note: Women not of childbearing potential are defined as: Any female who is post-menopausal [age $\geq$ 55 years with cessation of menses for 12 or more months or less than 55 years but not spontaneous menses for at least 2 years or less than 55 years and spontaneous menses within the past 1 year, but currently amenorrhoeic (e.g., spontaneous or secondary to hysterectomy), and with postmenopausal gonadotropin levels (luteinizing hormone and follicle-stimulating hormone levels > 40 IU/L) or postmenopausal estradiol levels (< 5 ng/dL) or according to the definition of "postmenopausal range" for the laboratory involved] or who have had a hysterectomy, bilateral salpingectomy, or bilateral oophorectomy).
- Sexually active subjects and their partners unwilling to use male or female latex condom or polyurethane condoms for patients with latex allergies to avoid potential viral transmission during sexual contact while on treatment and within 30 days after treatment with talimogene laherparepvec.
- Subject who is unwilling to minimize exposure with his/her blood or other body fluids

to individuals who are at higher risks for HSV-1 induced complications such as immunosuppressed individuals, individuals known to have HIV infection, pregnant women, or children under the age of 1 year, during talimogene laherparepvec treatment and through 30 days after the last dose of talimogene laherparepvec.

- Known previous history of sensitivity to talimogene laherparepvec or any of its components to be administered during dosing (e.g. sorbitol, myo-inositol)
- Hypersensitivity to pembrolizumab or any of its excipients.
- Has a history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.
- Prior therapy with talimogene laherparepvec, tumor vaccine.

- Prior chemotherapy, radiotherapy, biological cancer therapy, targeted small molecule therapy or major surgery within 21 days prior to study Day 1 or who has not recovered (i.e., to CTCAE ≤ grade 1 or at baseline) from adverse events due to previously administered therapy. Note: Subjects with ≤ grade 2 neuropathy and alopecia are an exception to this criterion and may qualify for the study. Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
- Is currently participating and receiving study therapy with another investigational device or study drug or has participated in a study of an investigational agent and received study therapy or used an investigational device within 3 weeks of the first dose of treatment.
- Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

- The presence of any other concurrent active malignancy.

7.0 RECRUITMENT PLAN

Both men and women and members of all races and ethnic groups are eligible for this trial. The clinical trial will be listed on the clinicaltrials.gov website and on the websites of participating institutions. Patients will be identified through internal referrals and external referrals by Medical and Surgical Oncologists, nationally and internationally. Patients will be recruited through the Sarcoma Disease Management Team of the Memorial Sloan Kettering Cancer Center. The Sarcoma Service and the Sarcoma Disease Management Team each hold weekly interdepartmental meetings to identify study participants for open clinical trials. We will also discuss the trial and patient recruitment with several Sarcoma patient support groups. The principal investigator will be available to all patients for further questions and information through a contact number, which will be provided on the consent form.

7.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent by following procedures defined in section entitled Informed Consent Procedures. During the registration process, registering individuals will be required to complete a protocol-specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed.

8.0 Informed Consent Procedures

The consent form/research authorization meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature, objectives, potential risks, and benefits of the intended study.

2. The length of study, what it entails, and the likely follow-up required.

3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)

4. The name of the investigator(s) responsible for the protocol.

5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

6. How the participants' data will be protected, who will have access to their PHI, and what data will be disclosed for research purposes

Prior to inclusion in the study and before protocol-specified procedures are carried out, the consenting professionals will explain the details of the protocol as outlined in the consent and research authorization to the participants/LARs. The participant/LAR will also be informed that they are free to withdraw from the study at any time. The consent discussion may occur in person or remotely via teleconference, telephone, or videoconference.

All participants/LARs must sign an IRB/PB-approved consent form/research authorization indicating their consent to participate. Each participant/LAR and consenting professional will sign and date the consent form. The participant/LAR must receive a copy of the signed informed consent form.

9.0 PRETREATMENT EVALUATION

Screening

All aspects of the screening evaluation should be completed prior to entering the study, unless otherwise noted:

Within 30 days of study start:

- Confirmation of disease: documented presence of metastatic and/or inoperable, locally advanced sarcoma with at least one palpable lesion deemed suitable for direct intralesional injection of talimogene laherparepvec and at least one target lesion. The palpable lesion may be used as the target lesion for RECIST assessment if it meets the RECIST 1.1 criteria for a target lesion and no other appropriate target lesion exists.
- All patients enrolled in this study will undergo a new baseline biopsy where feasible
- Informed Consent

Within 3 weeks of study start:

- Full medical history, physical exam, assessment of performance status by KPS or ECOG status
- Review of concomitant medications
- Complete vital signs (pulse, blood pressure, temperature, respiratory rate) as well as weight and height. Height may be documented at any time prior to registration.
- Standard baseline imaging with CT scan of the chest (with or without contrast), abdomen and pelvis (with contrast where renal function permits) and MRI if applicable. Additional imaging for research purposes may also be performed where clinically appropriate.
- 12-lead electrocardiogram (EKG)
- Serum β-HCG pregnancy test for women with child-bearing potential. (within 72 hours)
- Complete blood count with differential, including lymphocyte and eosinophil count.
- Comprehensive metabolic panel (glucose, blood urea nitrogen, creatinine, sodium, potassium, chloride, bicarbonate, calcium, total protein, albumin, serum bilirubin, alkaline phosphatase, ASL, AST), phosphorus, magnesium, TSH, T4 free, amylase, lipase.
- Review of inclusion and exclusion criteria

Please refer to Study Calendar in Section 10 for additional information.

9.0 TREATMENT/INTERVENTION PLAN

9.1 Study drugs

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in section 11.0. Modifications and dose delays due to toxicity are described further in section 11.3. The schedule of evaluations and interventions is described in Section 10.

Patients will be treated with up to 4mL at 10^6 pfu/mL of talimogene laherparepvec given on Week 1 and up to 4mL at 10^8 pfu/mL starting at Week 4 every 3 weeks thereafter.

Pembrolizumab at 200mg/dose will be given on Week 1 and every 3 weeks thereafter for up to 35 cycles. Patients will be reassessed at week 8 and then every 8 weeks until week 56 and then every 12 weeks thereafter or as per the discretion of the treating investigator .

Talimogene laherparepvec will be administered by intralesional injection into injectable lesions with or without image ultrasound guidance. The initial dose (Week 1) of talimogene laherparepvec is up to 4.0 mL of 10^6 plaque-forming units (PFU)/mL. Subsequent doses of talimogene laherparepvec are up to 4.0 mL of 10^8 PFU/mL. When talimogene laherparepvec and pembrolizumab are administered on the same day, talimogene laherparepvec must be administered first.

Pembrolizumab at a dose of 200mg will be administered intravenously on Week 1 and every 3 weeks (±3 days). Pembrolizumab infusion should be administered in 30 minutes, with a window of -5 and +10 minutes, using an infusion pump.

No additional investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

9.1.1 Dose rationale

The toxicity profile of talimogene laherparepvec used as single agent based on the same proposed dose was well studied in early phase clinical trials as well as in a large, randomized phase III trial in patients with melanoma.[51, 49, 50] In a phase 1b/2 trial also in patients with melanoma using the same doses of talimogene laherparepvec in combination with ipilimumab, although Grade 3/4 adverse events occurred in 32% of the patients, only 2 patients had possible immune-related grade 3 or 4 adverse events and no DLTs were reported.[71] In addition, a Phase Ib/II study of the combination of talimogene laherparepvec and pembrolizumab in patients with melanoma has recently completed accrual. In this study, talimogene laherparepvec was administered five weeks prior to initiating pembrolizumab. Patients were given intratumoral talimogene laherparepvec injection at doses up to 4 mL per treatment (10^6 PFU/mL on day 1, then 10^8 PFU/mL on day 22 and every 2 weeks thereafter. Intravenous pembrolizumab was given at a dose of 200mg from Day 36 in phase 1b (n = 20) and Day 1 in phase 2 (n = 90) and then every two weeks thereafter. The combination appeared to be safe and well tolerated.[92].[2] The FDA has now approved pembrolizumab, administered intravenously at a dose of 2mg/kg every 3 weeks, for the treatment of patients with unresectable and metastatic melanoma. Intralesional injection of talimogene laherparepvec, also known as IMLYGIC®, has been approved by the United States Food and Drug Administration (FDA) for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in adult patients with melanoma recurrent after initial surgery. However, it has not been shown to increase OS or have an effect on metastases to internal organs including the liver and lungs.
The suggested treatment plan is summarized in Table 4. Patients will be offered an optional biopsy at the time of progression of disease.

Table 4. Study design and treatment plan

	Talimogene laherparepvec	Pembrolizumab
One stage design based on the exact binomial test	Intratumoral administration (injection): : Up to 4mL at 10^6 pfu/mL at Week 1 Up to 4mL at 10^8 pfu/mL at Week 4 and every 3 weeks thereafter.	Dose: 200mg/dose at Week 1, and every 3 weeks thereafter.

Toxicities will be assessed using the NCI CTCAE (version 4.03) unless otherwise specified and discussed in detail in section 11.0.

9.2 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment with intralesional talimogene laherparepvec may continue until one of the following criteria applies:

- Disappearance of injectable lesions
- Complete response
- Confirmed progression of disease (detailed in section 13) or clinical progression
- Intercurrent illness that prevents further administration of treatment
- Intolerance of study treatment (detailed in section 11.1)
- Completion of 35 treatments (approximately 2 years) with pembrolizumab
    - Note: The number of treatments is calculated starting with the first dose. Participants who stop the combination or pembrolizumab after receiving 35 doses may be eligible for retreatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 9.2.1. Participants may be retreated in the Second Course Phase (Retreatment) for up to an additional 17 cycles (approximately 1 year).

- Patient is lost to follow-up
- Physician's decision to withdraw a patient from the study for a reason not listed
- Patient decides to withdraw from the study
- End of study, whichever occurs first.

In the absence of treatment delays due to adverse events, treatment with pembrolizumab may continue until one of the following criteria applies:

- Confirmed progression of disease (detailed in section 13) or clinical progression
- Intercurrent illness that prevents further administration of treatment
- Intolerance of study treatment (detailed in section 11.1)
- Patient is lost to follow-up
- Completion of 35 treatments (approximately 2 years) with pembrolizumab
    - Note: The number of treatments is calculated starting with the first dose. Participants who stop the combination or pembrolizumab after receiving 35 doses may be eligible for retreatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 9.2.1. Participants may be retreated in the Second Course Phase (Retreatment) for up to an additional 17 cycles (approximately 1 year).
- Physician's decision to withdraw a patient from the study for a reason not listed
- Subject is lost to follow-up
- Patient decides to withdraw from the study
- End of study, whichever occurs first.

Subjects with a complete response (CR) may stop injections of talimogene laherparepvec, but treatment with pembrolizumab will be continued unless one of the criteria for treatment discontinuation is met. This is discussed in again in section 13.0.

Due to the mechanism of action, subjects may experience growth in existing tumors or the appearance of new tumors prior to maximal clinical benefit of talimogene laherparepvec and pembrolizumab. The patient may be allowed to continue study treatment after initial RECIST 1.1 defined progression if they are assessed by the treating physician to be deriving clinical benefit and tolerating study treatment. The treating physician may consult with the overall study PI for help with assessing the patient. Such patients should discontinue study therapy upon further evidence of progression.

9.2.1 Second Course

All participants in the inoperable, locally advanced/metastatic cohort who stop study treatment with SD or better may be eligible for up to an additional 17 cycles (approximately 1 year) of pembrolizumab and talimogene laherparepvec treatment if they progress after stopping study treatment from the initial treatment phase and have lesions that are eligible for injection as defined in the inclusion criteria. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the participant meets the following conditions:

Either

- Stopped initial treatment with study treatment after attaining an investigator-determined confirmed CR based on RECIST 1.1, and
    - Was treated with at least 8 cycles of study treatment before discontinuing treatment, and
    - Received at least 2 treatments with pembrolizumab beyond the date when the initial CR was declared

OR

- Had SD, PR, or CR and stopped study treatment after completion of 35 administrations (approximately 2 years) of study treatment for reasons other than disease progression or intolerability

AND

- Experienced an investigator-determined radiographic disease progression by RECIST 1.1 after stopping initial treatment, and
    - Have at least 1 injectable cutaneous, subcutaneous (superficial or deep) soft tissue or nodal lesion ≥ 10 mm in longest diameter as defined in the inclusion criteria.
    - No new anticancer treatment was administered after the last dose of study treatment, and
    - The participant meets all of the safety parameters listed in the inclusion criteria and none of the safety parameters listed in the exclusion criteria, and

- The study is ongoing

An objective response or disease progression that occurs during the Second Course Phase for a participant will not be counted as an event for the primary analysis of either endpoint in this study.

**Note: patients must have measurable disease at the start of protocol treatment to be eligible for this provision.*

9.3 General Concomitant Medication and Supportive Care Guidelines

Supportive Care: Best supportive care and treatment will be given as appropriate to each subject as per Clinical Center and ASCO guidelines (antiemetics, antibiotics, packed red blood cell and platelet transfusions, nutritional support, non-radiation palliative treatment for pain).

Steroids:

Doses up to 10mg of prednisone daily (or equivalent) will be allowed concurrently with continuous treatment with talimogene laherparepvec and/or pembrolizumab. If the subject requires corticosteroid dosing of >10 mg prednisone daily (or equivalent) and/or other immunosuppressive medication for related toxicities, talimogene laherparepvec and pembrolizumab dosing must be held until the corticosteroid dose has decreased to ≤10 mg prednisone daily (or equivalent) and the administration of the other immunosuppressive medication has discontinued. In the setting of non-immune mediated indications for use, chronic/active low dose steroid use (at doses >10 mg prednisone daily) may be permitted at the discretion of the principal investigator.

Radiation: Radiation therapy is only allowed during the study if required for palliation of symptoms due to underlying sarcoma.

Surgery: Subjects must not schedule any elective surgeries during the treatment period and for at least 30 days after the last administration of study drugs. If a subject undergoes any unexpected surgery during the course of the study, all study treatments must be withheld and the investigator or designee should report the event per their institutional guidelines. A subject may be allowed to resume study drugs per PI's discretion.

Other supportive measures and specific treatments/guidelines recommended for the management of toxicities are detailed in Appendix A.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

10.1 – Pre-treatment diagnosis confirmation

All patients will have histological confirmation of their diagnosis prior to treatment. Baseline clinical and radiologic evaluations are to be conducted within 3 weeks of starting protocol therapy. In addition, a mandatory baseline biopsy will be performed within 30 days of first dose of the study drugs for all patients enrolled in the study where feasible.

10.2 – Standard evaluations

Locally advanced/metastatic cohort

Evaluations at clinic visits will occur at weeks 1 and 4 (± 3 days), and then prior to every scheduled treatment (± 3 days) thereafter. Patients who achieve response/stability of disease lasting for at least 12 months and come off study therapy will be followed every 2 months (± 2 weeks) thereafter. Imaging studies will be performed at baseline, week 8 and every 8 weeks subsequently (± 1 week window) until 56 weeks, and then every 12 weeks thereafter or as per the discretion of the treating investigator. The clinical evaluations are delineated further in the study calendar (Table 6) and include:

- Full medical history, physical exam, assessment of performance status by KPS or ECOG status
- Review of concomitant medications
- Complete vital signs (pulse, blood pressure, temperature, respiratory rate) as well as weight and height. Height may be documented at any time prior to registration.

All patients will undergo a baseline staging CT scan of the chest (with or without contrast), abdomen and pelvis (with contrast where renal function permits), and MRI abdomen/pelvis (with and without contrast) if deemed necessary by the treating physician. Response evaluations will occur at week 8 and every 8 weeks subsequently (± 1 week window) until 56 weeks, and then every 12 weeks thereafter or as per the discretion of the treating investigator. EKGS will also be performed at baseline, week 8 and every 8 weeks thereafter to evaluate the heart during the study.

Routine/standard blood samples will be obtained at screening, weeks 1, 4 and then prior to every scheduled treatment (±3 days) thereafter. All routine blood samples should be obtained prior to the daily dose talimogene laherparepvec and/or pembrolizumab. These samples will be used for routine tests and are part of standard of care. The following analyses will be assessed at various time points during the study:

- **Hematology:** Complete blood count with differential, including lymphocyte and eosinophil count.
- **Chemistry:** phosphorus, magnesium
- Serum β-HCG pregnancy test for women with child-bearing potential (NOTE: for women of child bearing potential a negative urine or serum pregnancy at screening and within 72 hours prior to first dose of study medication is required.
- Comprehensive metabolic panel (sodium, potassium, chloride, bicarbonate, calcium, glucose, blood urea nitrogen, creatinine, total protein, albumin, serum bilirubin, alkaline phosphatase, ALT, AST)
- TSH, T4 free.
- Additional tests if clinically indicated.

10.2.1 Required Laboratory Parameters for Treatment

A new dose of therapy may be initiated provided that the patient meets the following criteria within 72 hours of treatment:

- ANC ≥ 1,000/μL

- Platelets > 75,000/μL
- All grade ≥ 2 non-hematologic adverse events (except for fatigue, nausea and vomiting, or laboratory values that are not clinically significant) must have resolved to CTCAE grade ≤ 1
- No evidence of infection/necrosis or local complications in the injection site.

10.3 – Tumor and blood samples for correlative/companion studies
All patients enrolled on this study will undergo paired biopsies/blood samples for research purposes (correlative/companion studies)

Metastatic/inoperable, locally advanced cohort:
Blood samples for research purposes will be obtained at week 1, 4, 7, 13, 19, 22 and at the date of the off study visit (± 7 days). This is detailed in Table 6 (Study calendar).
Biopsies for research purposes will be done at baseline (within 30 days of the first dose of talimogene laherparepvec and/or pembrolizumab) and at Week 8 in all patients enrolled in this study where feasible. Biopsy of a distant site of disease at each biopsy timepoint will be obtained. A site not intended to be injected is preferred for biopsy where feasible. Up to 6 cores from each tumor biopsy site should be taken where feasible and safe to do so. A goal of 6 cores should be obtained with a minimum of one formalin-fixed, one fresh and one flash frozen in liquid nitrogen. Biopsy procedures will otherwise be performed in accordance with institutional guidelines and the biopsy guideline outlined in Appendix F. An optional biopsy of a distant site of disease will be offered to all patients at the time of progression.

Neoadjuvant cohort:
Blood samples for research purposes will be obtained at week 1, 4, and week 6 and 12 (where applicable) prior to surgical resection. For patients receiving additional cycles of treatment, additional blood samples will be drawn prior to each cycle.
Mandatory biopsies for research purposes will be done at baseline (within 30 days of the first dose of talimogene laherparepvec and/or pembrolizumab) and at Week 4 prior to the administration of study therapy. For patients receiving additional cycles of treatment, additional core biopsies may be obtained prior to each additional treatment (ie. week 7 and week 10, etc.)
An open excisional biopsy or up to 6 cores from each tumor biopsy site should be taken where feasible and safe to do so. A goal of 6 cores should be obtained with a minimum of one formalin-fixed, one fresh and one flash frozen in liquid nitrogen. Biopsy procedures will otherwise be performed in accordance with institutional guidelines and the biopsy guideline outlined in Appendix F.

<u>Tumor Based Biomarkers</u>

Interrogation of immune responses within the tumor microenvironment of sarcomas before and after treatment with talimogene laherparepvec and PD-1 checkpoint blockade.

For each resected specimen, up to 6 cores of tissue will be obtained for tumor immune correlative studies.

a) **Density of immune infiltration and immune checkpoint expression of sarcomas:** IHC will be used to assess the number and composition of immune infiltrates in order to define the immune cell subsets present within the tumor and PD-L1 protein expression by IHC before and after exposure to talimogene laherparepvec and pembrolizumab.

   The IHC assays will be performed using but are not limited to the following markers: CD3, CD4, CD8, CD25, CD28 CD45RA, CD68, CD69, CCR7, PD-L1, PD-1, CD137, FOXP3, LAG-3, TIM-3, and ICOS.

   PD-L1 expression by immunohistochemistry staining of archival tumor specimens will be performed with using a QualTek immunohistochemistry-based assay.

b) **Phenotype and function of TIL in human sarcomas:**
   Multiparameter flow cytometry (MFC) performed on freshly dissociated tumor tissue will be used to characterize the tissue T cell populations. We will study the functional significance of PD-1 expression on T cells isolated from sarcomas. Using intracellular cytokine staining (ICS) and MFC analysis on freshly isolated TIL, we will identify the T cell cytokine profiles in accordance to their immune checkpoint expression profile (PD-1, LAG-3, TIM-3). A range of cytokines representing key lymphocyte subgroups (e.g., Th1, 2 or 17) such as IL-2, TNF□ , IFN-□ IL-17 among other inflammatory mediators will be assessed. Functional T cell markers including granzyme B and perforin as well as activation markers such as CD62L, CD44, CD69 will be also included in our analysis.

c) **Tumor Biopsy gene expression profiling**: Fresh tumor biopsy will be examined for RNA gene and protein expression by NanoString technology (nCounter® RNA: Protein, PanCancer Immune Profiling Panel) and/or qRT-PCR to detect expression of immune related genes. This panel includes 770 immune related genes including: 109 genes related to cell surface markers for 24 different immune cell types and populations, 30 genes for commonly studied cancer/testis (CT) antigens, over 500 genes for measuring immune response and 40 reference genes.

d) **Neoantigen analysis:** Massively parallel sequencing of the whole exome of the tumor tissue and normal blood will be performed for patients who opt in. Genomic DNA will be captured via solution-based hybrid selection and sequenced on the Illumina HiSeq platform by the Genomics Core at MSKCC. The sequencing data will be aligned by the Bioinformatics Core Tumor, using Somatic Sniper, Somatic Indel Detector and Mutect softwares.

e) **Next generation sequencing for T-cell receptor clonality in tumor-infiltrating lymphocytes (TIL):** Samples will be analyzed using high throughput sequencing of the variable β-chain of the T cell receptor (TCR) to characterize the expansion and clonality of the T-cell repertoire in TILs.

f) **Tumor Biopsy Analyses:** Tissue microarrays (TMA) will be created using biopsy tissue mounted on poly-L-lysine coverslips, done by central pathology. Deidentified TMAs will be shipped to Enable Medicine for imaging analysis.

Role of Enable Medicine as a Participating Site is as Follows:

- Specimens will be labeled with deidentified study IDs, to only indicate cohort identification and patient subsets.
- Documents will be sent with a simple packing sheet providing an inventory list of the material being sent.
- No participant identifiers will be shared.
- Specimens will be shipped to Enable Medicine, located at 3499 Edison Way, Menlo Park, CA 94025.
- Specimens will be shipped at ambient temperature.
- Specimens are being tracked in a secure MS Excel that has been locked.
- Specimens should be received during normal business hours, M-F.
- Enable Medicine's primary contact is as follows, and will be notified when shipments go out – and to confirm shipment receipt
    - Archit Sheth-Shah (archit@enablemedicine.com)
- Preferred Courier is FedEx

g)

Peripheral blood studies

Blood samples will be taken prior to initiation of study therapy and on designated time points post-treatment. Research blood collection procedures will be performed as outlined in Appendix F.

These samples will be analyzed for:

a.) Immunophenotyping and Functional Analyses:

1. Samples will be analyzed by flow cytometry to study the effects of talimogene laherparepvec and pembrolizumab on various peripheral blood immune cell subsets including, but not limited to T cell subsets (activated, memory and regulatory T cells).

2. To explore whether PD-1 blockade will restore T cell activation and function, peripheral blood mononuclear cells (PBMCs) will be isolated and cryopreserved.

Assays of the functional status of effector T cells will be performed, including, but not limited to assays for interferon-gamma (IFN-γ) and granzyme B. This assay will use a non-specific stimulus including but not limited to anti-CD3 and anti-CD28 and would allow for the comparison of the effect of nivolumab on T cell function.

b.) Soluble Factors: Baseline and on-treatment serum levels of chemokines, cytokines and other immune mediators will be assessed by techniques that may include but are not limited to ELISA or multiplex assays. Analytes may include, but are not limited to IFN-γ, IL-12, IL-10, soluble MICA, C-reactive protein, soluble PD-1 and soluble PD-L1.

c.) Next generation sequencing for T-cell receptor clonality in peripheral blood: Samples will be analyzed using high throughput sequencing of the variable β-chain of the T cell receptor (TCR) to characterize the expansion and clonality of the T-cell repertoire in peripheral blood mononuclear cells.

Table 5. Exploratory Biomarkers

Biomarker name	Assay	Tissue/Body Fluid Tested and Timing of Assay
Peripheral Blood Cells	1. Flow cytometric analyses to evaluate activated (HLA-DR+) and memory (CD45RA-) T cells 2. Flow cytometric analyses to evaluated peripheral blood leucocytes including CD4/CD25/FoxP3, CD4/CD8/CD45RA/CCR7, CD4/CD8/LAG3/PD-1/PD-L1, CD4/CD8/CD137 3. Functional Status of effector T cells assays for interferon-gamma and granzyme B. 4. T-cell subsets and their activation status (CD8+ Teff/Treg ratio and ICOS expression	Metastatic/locally advanced cohort: Blood (Weeks, 1,4, 7, , 13, 19, 22 and off-study) Neoadjuvant cohort: blood (weeks 1, 4, 6 and 12 where applicable) and prior to all cycles of therapy
Soluble Factors, Serum	Treatment modulation of serum levels of chemokines, cytokines and other immune mediators by ELISA or other multiplex-based assay methods. Primary analysis includes interferon-gamma and IL-10.	Metastatic/locally advanced cohort: Blood Serum (Weeks 1,4, 7, , 13, 19, 22 and off-study) Neoadjuvant cohort: blood (weeks 1, 4, 6 and 12 where applicable) and prior to all cycles of therapy
Characterization of Tumor infiltrating lymphocytes	1. IHC to assess number and composition of	Metastatic/locally advanced cohort:

	immune infiltrates to define immune cell subsets present within tumor before and after exposure to treatment. CD3, CD4, CD8 and FOXP3 will be evaluated. 2. Immune cell phenotyping of freshly isolated TIL to evaluate Treg/Teff ratio (CD8+/FoxP3+ cells) and activations markers (ICOS, PD-1, CD69).	Tumor biopsy at: Baseline Week 8 Progression (optional) Neoadjuvant cohort: Tumor biopsy at: Baseline Week 4 Week 7 and/or 10 if applicable (optional) Surgical specimen
PD-L1 expression by IHC	Qualtek immunohistochemistry-based assay for PD-L1	Metastatic/locally advanced cohort: Tumor biopsy at: Baseline Week 8 Progression (optional) Neoadjuvant cohort: Tumor biopsy Baseline Week 4 Week 7 and/or 10 if applicable (optional) Surgical specimen
Tumor Biopsy neoantigen analysis	Fresh frozen tumor biopsy will be utilized for massively parallel whole exome sequencing. Available databases such as SNP effect (http://snpeff.sourceforge.net/will be used to determine which mutations are in coding regions and will affect amino acid sequence. NetMHC and the Immune Epitope Database will be utilized to predict MHC Class I binding and T cell interactions, respectively.	Tumor biopsies at baseline Paired normal peripheral blood mononuclear cells at baseline
T-cell receptor sequencing	High throughput sequencing of the variable β chain of the T-cell receptor.	Metastatic/locally advanced cohort: Tumor biopsy at:

		Baseline Week 8 Progression (optional) Neoadjuvant cohort: Tumor biopsy at: Baseline Week 4 Week 7 and/or 10 if applicable (optional) Surgical specimen

10.4 – Imaging studies for exploratory analysis of diagnosis and non-invasive, monitoring of disease during therapy

In addition to invasive interrogation of immune responses within the tumor microenvironment, imaging studies are planned to evaluate the potential for noninvasive monitoring of disease and disease progression in patients with cutaneous disease. All imaging modalities are FDA approved or have been granted FDA exemption and are believed to involve minimal risk to participants.

RECIST 1.1 criteria for cutaneous disease currently relies on caliper measurements and clinical photography with rulers to monitor disease response to therapy. For each patient with cutaneous disease, imaging will be performed of the injected and distant sites of metastasis (if accessible) for the purposes of correlative studies both at baseline and at regular intervals. These imaging techniques will be performed prior to biopsy for the purposes of correlative studies and in order to decrease the possible effect on the biopsies on imaging results. Imaging to include reflectance confocal microscopy, optical coherence tomography, and ultrasonography if feasible (as determined by the investigator) will be performed. These imaging modalities are intended both to enhance our understanding of the tumor response to therapy and to provide a much-needed addition to the literature

Briefly, confocal microscopy uses light that is back-scattered from the tissue. The penetration depth can be limited which is why combination with optical coherence tomography or ultrasonography may be important for identifying tumor volumes or morphology. While CLSM provides higher resolution and cellular level detail than OCT, the images can be difficult to interpret because of their en face orientation and lack of structural context (e.g., epidermis versus dermis). Thus, the addition of OCT and/or ultrasonography is anticipated to facilitate interpretation of our CSLM images. In the long term, we expect that addition of OCT and ultrasonography to CLSM will enable noninvasive and real-time monitoring of sarcoma response to immunotherapy. High frequency ultrasonography with Doppler based assessment of tissue blood flow and elastography will be attempted if available on a case by case basis to further enhance our understanding of tumor response to therapy.

Table 6. Study calendar

A. Metastatic/locally advanced cohort

	Screening	Week 1	Week 4	Week7	Week 8	Week 10	Week13 and every 3 weeks up to 24 months	Off study visit[10]
Talimogene laherparepvec[1]		X	X	X		X	X	
Pembrolizumab[1]		X	X	X		X	X	
Informed consent	X							
Review of concomitant medications	X	X	X	X		X	X	X
Review of adverse events		X	X	X		X	X	X
Physical exam	X	X	X	X		X	X	X
Routine laboratory tests[6]	X	X	X	X		X	X	X
Research blood [4,]		X	X	X			X[4]	X
Hepatitis B, C and HSV screen[9]	X							
Pregnancy Test[7]	X	X						X
EKG[3]	X				X[3]			X
CT and/or MRI[2]	X				X[2]			

Additional imaging for research purposes[11]	X				X			
Biopsy	X				X[5]			
Reporting Exposure to talimogene laherparepvec (subject's household member or caregiver or healthcare provider)[8]	X	X	X	X		X	X	X
Swab collection from suspected herpes infected lesions for T-VEC DNA qPCR testing		X	X	X	X	X	X	X

1. Talimogene laherparepvec and pembrolizumab will be given at the assigned doses.
2. Standard Imaging studies will be performed at baseline, week 8 and every 8 weeks subsequently (± 1 week window) and will include CT of chest (with or without contrast) , CT of abdomen/pelvis (with contrast where renal function permits) and/or MRI abdomen/pelvis (with and without contrast), in addition to imaging of the affected area if deemed necessary by the study investigator.
3. An EKG will be performed at baseline, week 8 and every 8 weeks subsequently (± 1 week window).
4. Research blood samples will be collected at week 1,4, 7, 13, 19, 22 and at the date of the off study visit (± 7 days).
5. Mandatory tumor tissue biopsies, of a distant site of disease, preferably a site not intended to be injected with talimogene laherparepvec where feasible, will be required at baseline and at week 8 (± 7 days). An optional biopsy at time of progression of disease will also be offered.
6. Routine laboratory tests include: cbc with differential, PT/INR and aPTT, comprehensive serum chemistry panel (including glucose, blood urea nitrogen, creatinine, sodium, potassium, chloride, bicarbonate, calcium, total protein, albumin, serum bilirubin, alkaline phosphatase, ALT, AST, phosphorus, magnesium, TSH, T4 free) urinalysis
7. Serum β-HCG (Female subject of childbearing potential should have a negative serum pregnancy at screening and within 72 hours prior to first dose of both study drugs and at the off study visit).
8. Exposure cases to be reported during the duration of the study and for 30 days post treatment. If the exposed individual is reporting signs or symptoms suspected to be related to talimogene laherparepvec exposure, the exposed individual may be asked to have a swab taken at baseline, during treatment and in follow-up to evaluate for the presence of talimogene laherparepvec DNA in the suspected herpetic lesion by qPCR testing.
9. Hepatitis serology includes testing for HCV antibody, HBV core antibody and HBV surface antigen.
10. The off study visit will take place 30 days (+7 days) after the last dose of talimogene laherparepvec or the last dose of pembrolizumab, whichever is later .
11. Additional imaging for research purposes will be performed in patients with cutaneous disease. Research imaging techniques will be performed at baseline and prior to treatment biopsies and then regularly in conjunction with the schedule when standard cross sectional imaging is performed.

11.0 TOXICITIES/SIDE EFFECTS

Toxicity will be assessed using the NCI CTCAE (version 4.03).

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value must be followed until resolution or stabilization of the event. As described in section 11.1, a dose delay >9 weeks may require the patient to be discontinued from the study, with exception of patients who undergo surgery.

11.1 Adverse Event Characteristics and Definitions

11.1.1 Definitions of Treatment Related Toxicity Events (TRTE) and decisions based on TRTEs:

Subjects are considered evaluable for feasibility and toxicity assessments if they receive at least one dose of the protocol-assigned dose(s). The treatment related toxicity events that determine feasibility and early-stopping results are defined as those that result in:

i) study drug(s) discontinuation or

ii) delay in study drug administration more than 9 weeks from the date of the planned dose (i.e., approximately 12 weeks since the previous dose)

TRTE will be evaluable throughout the study period. The events will only be considered TRTE if judged by the investigator to be related to the administration of talimogene laherparepvec and/or pembrolizumab.

Examples include

- Grade 4 non-hematologic toxicity
- Grade 3 or greater immune-mediated adverse events (except skin).
- Any grade plasmacytoma at or near the injection site or evidence of impaired wound healing at the injection site
- Grade 3 or greater allergic reactions considered at least possibly related to talimogene laherparepvec or pembrolizumab.
- Grade 3 or higher pneumonitis
- Grade 3 non-hematologic toxicity lasting > 3 days despite optimal supportive care
- Any grade 3 or higher non-hematologic laboratory value if:
    - medical intervention is required, or
    - the abnormality leads to hospitalization, or
    - the abnormality persists for > 1 week
- Febrile neutropenia grade 3 or grade 4.
- Thrombocytopenia < 25 x 10^9/L
- Grade 5 toxicity (i.e., death)

The following herpetic events:

- Serious herpetic events such as herpetic encephalitis, encephalomyelitis or disseminated herpetic infection
- For any herpetic events confirmed due to talimogene laherparepvec that require treatment with acyclovir or similar anti-viral agent, treatment with talimogene laherparepvec should be suspended if anti-viral treatment is required with systemic acyclovir or other anti-virals, and if ongoing anti-viral treatment is required, treatment with talimogene laherparepvec 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 (as confirmed by PCR testing) should not be considered as treatment related toxicity event caused by talimogene laherparepvec.
Subjects may be replaced if they are not evaluable for feasibility and treatment related events (e.g., a subject did not receive both study drugs or permanently discontinued talimogene laherparepvec prior to receiving the first dose of pembrolizumab for any reason).

If dosing is delayed by more than 9 weeks from the date of the planned dose (i.e., approximately 12 weeks since the previous dose) due to the occurrence of an adverse event that is considered related to talimogene laherparepvec and/or pembrolizumab, then the subject should be taken off study treatment(s) that the adverse event is deemed to have been related to (see section 11.4.1).

11.1.2 Definition of an AE

Any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits, abuse, or misuse. Examples of events meeting the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or grade of the condition
- New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE).

Events that do not meet the definition of an AE include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

11.1.3 Definition of a SAE

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

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- 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

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment. SAE reporting is required for 30-days after the participant's last investigational treatment. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

11.1.4 Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis), or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements) including those that worsen from baseline, and events felt to be clinically significant in the medical and scientific judgment of the investigator are to be recorded as an AE or SAE, in accordance with the definitions provided.
However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are not to be reported as AEs or SAEs.

11.1.5 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

Disease Related Events are events (serious or non-serious) anticipated to occur in the study population due to the underlying disease. These could include overall disease progression or pain or discomfort caused by growing tumors. Such events do not meet the definition of an Adverse Event unless assessed to be more severe than expected for the subject's condition.

An event which is part of the natural course of the disease under study (i.e., disease progression) does not need to be reported as an SAE. Deaths and hospitalizations related to disease (other than for study procedures) during the study period and 30 days after completion must be reported as SAEs.

Disease Related Events that would qualify as an Adverse Event or Serious Adverse Event:

- An event based on the underlying disease that is worse than expected as assessed by the investigator for the subject's condition
- The investigator believes there is a causal relationship between the investigational product(s)/study treatment/protocol required therapies and disease worsening

11.2 – Risks, toxicities and adverse drug reactions – talimogene laherparepvec

Talimogene laherparepvec dosing likely will produce side effects, and not all side effects may be known. Specific identified risks and potential risks are highlighted below, as well as adverse drug reactions observed in clinical trials.

As of 26 April 2018, an estimated 1253 subjects (727.1 subject-years) have been exposed to talimogene laherparepvec in Amgen-sponsored clinical studies since the beginning of the development program. Overall, most adverse events reported in subjects administered talimogene laherparepvec are non-serious and primarily include flu-like symptoms and injection site reactions. Most fatal adverse events reported in subjects administered talimogene
laherparepvec were reported in the setting of disease progression. Please refer to talimogene laherparepvec investigational brochure (Appendix A) for additional information.

11.2.1 –Important Identified risks – talimogene laherparepvec

Disseminated herpetic infection in severely immunocompromised individuals (those with any severe congenital or acquired cellular and/or humoral immune deficiency)

Talimogene laherparepvec has not been studied in immunocompromised subjects. Based on animal data, subjects who are severely immunocompromised (eg, subjects 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 *[see Section 2.0: Contraindications and Section 7.0 of the Investigator's Brochure].* Disseminated herpetic infection may also occur in immunocompromised subjects (such as those with HIV/AIDS, leukemia, lymphoma, common variable immunodeficiency, or who require chronic high-dose steroids or other immunosuppressive agents). Consider the risks and benefits of treatment before administering talimogene laherparepvec to these subjects.

- Accidental exposure of healthcare providers (HCP) to Talimogene Laherparepvec

  Accidental exposure may lead to transmission of talimogene laherparepvec and herpetic infection. Healthcare providers and close contacts (household members, caregivers, sex partners or persons sharing the same bed), pregnant women and neonates should avoid direct contact with injected lesions or body fluids of treated subjects. Accidental needle stick and splash back have been reported in healthcare providers during preparation and administration of talimogene laherparepvec. Subjects should be advised to avoid touching or scratching injection sites as this could lead to inadvertent transfer of talimogene laherparepvec to other areas of their body. Close contacts who are pregnant or immunocompromised should not change the subject's dressings or clean their injection sites.

  Caregivers should be advised to wear protective gloves when assisting subjects in applying or changing dressings and to observe safety precautions for disposal of used dressings and cleaning materials [see *Special Instructions for Use and Handling of the investigational brochure].*

  In the event of an accidental exposure to talimogene laherparepvec, exposed individuals should be advised to clean affected area thoroughly with soap and water and/or a

disinfectant. If signs or symptoms of herpetic infection develop, they should contact their healthcare provider. Talimogene laherparepvec is sensitive to acyclovir.

Obstructive airway disorder

Obstructive airway disorder has been reported following talimogene laherparepvec treatment. Use caution when injecting lesions close to major airways.

- Immune-mediated adverse events
  In clinical studies, immune-mediated events including glomerulonephritis, vasculitis, pneumonitis, worsening psoriasis, and vitiligo have been reported in subjects treated with talimogene laherparepvec.
  Consider the risks and benefits of talimogene laherparepvec before initiating treatment in subjects who have underlying autoimmune disease or before continuing treatment in subjects who develop immune-mediated events.

- Plasmacytoma at the injection site
  Plasmacytoma has been reported in proximity to the injection site after administration of talimogene laherparepvec. Consider the risks and benefits of talimogene laherparepvec in subjects with multiple myeloma or in whom plasmacytoma develops during treatment.

- Cellulitis at site of injection
  Necrosis or ulceration of tumor tissue may occur during talimogene laherparepvec treatment. Cellulitis and systemic bacterial infection have been reported. Careful wound care and infection precautions are recommended, particularly if tissue necrosis results in open wounds.

- Arterial hemorrhage
  Fatal carotid arterial hemorrhage (carotid blowout syndrome) has been reported following administration of talimogene laherparepvec in the setting of recurrent squamous cell carcinoma of the head and neck (SCCHN). Subjects with tumor(s) in direct contact or encasing a major blood vessel with ulceration and/or fungation onto the skin surface, and subjects with history of re-irradiation to a field which involves the carotid arteries may be at increased risk for arterial hemorrhage. Consider the risks and benefits of treatment before administering talimogene laherparepvec to these subjects.

- Herpetic infection
  In clinical studies, herpetic infections (including cold sores and herpes keratitis) have been reported in subjects treated with talimogene laherparepvec. Subjects who develop herpetic infections should be advised to follow standard hygienic practices to prevent viral transmission.
  Talimogene laherparepvec is sensitive to acyclovir. Consider the risks and benefits of talimogene laherparepvec treatment before administering acyclovir or other anti-viral agents indicated for management of herpetic infection. These agents may interfere with the effectiveness of talimogene laherparepvec

- Impaired healing at the injection site
  In clinical studies, impaired healing at the injection site has been reported. Talimogene laherparepvec may increase the risk of impaired healing in subjects with underlying risk

factors (eg, previous radiation at the injection site or lesions in poorly vascularized areas). Consider the risks and benefits of talimogene laherparepvec before continuing treatment if persistent infection or delayed healing develops.

11.2.3 Herpetic Events and qPCR Testing

- Any cases of suspected herpetic events in treated subjects or of suspected secondary transmission in a close contact or HCP **with signs or symptoms** should be reported to Amgen within 24 hours of sponsor awareness.
- All reporting is done over the phone to Amgen at (855-465-9442). Refer to Appendix C and table 12 for reporting suspected herpetic events, and a sample form with the information to be reported to Amgen. Patients will be tested if they develop suspected herpetic lesions in order to allow detection of DNA specific to talmogene laherparepvec.
    - Any suspected herpetic lesion should be evaluated by the investigator and swabbed
    - Swabs of cold sores, vesicles or any other lesions suspected to be herpetic in origin should be obtained.
    - Follow the instructions provided by the qPCR test manual provided for sample collection, shipping, and handling process, (appendix B)
    - Amgen does not require qPCR or other testing for wild type HSV 1. A commercially available test should be ordered if the investigator believes it is clinically indicated.
    - Principal investigator/clinical research team should report confirmed (by qPCR as described) herpetic events to local institutions Infection Control Department.
- Patients will be provided with a letter detailing exposure, prevention, and who to contact if a family member, care giver, or close contact experiences symptoms that may be related to talimogene laherparepvec.

11.2.4 - Adverse Drug Reactions – talimogene laherparepvec

The most commonly reported adverse reactions (≥ 25%) in talimogene laherparepvec -treated subjects were fatigue, chills, pyrexia, nausea, influenza like illness, and injection site pain. Most adverse reactions reported were mild or moderate in severity and generally resolved within 72 hours. The most common grade 3 or higher adverse reaction was cellulitis. Pyrexia, chills, and influenza like illness can occur any time during talimogene laherparepvec treatment, but were reported more frequently during the first 3 months of treatment, particularly in subjects who were HSV-1 negative at baseline.

Adverse drug reactions observed in talimogene laherparepvec clinical trials are listed below in table 7.

Table 7. ADRs Observed in talimogene laherparepvec Clinical Trials

		Imlygic (N = 292)			
			Events with Severity		
System Organ Class Preferred Term	CIOMS Frequency	All Events n (%)	Grade 3-4 n (%)	Grade 5 n (%)	Serious Events n (%)
Number of Subjects reporting treatment-emergent adverse events	Very Common	290 (99.3)	94 (32.2)	11 (3.8)	75 (25.7)
Infections and infestations					
Cellulitis	Common	17 (5.8)	6 (2.1)	0 (0)	7 (2.4)
Oral herpes	Common	14 (4.8)	0 (0)	0 (0)	0 (0)
Incision site infection	Uncommon	2 (< 1)	0 (0)	0 (0)	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)					
Tumour pain	Common	22 (7.5)	5 (1.7)	0 (0)	4 (1.4)
Infected neoplasm	Common	8 (2.7)	3 (1.0)	0 (0)	3 (1.0)
Plasmacytoma[1]	Uncommon	1 (< 1)	1 (< 1)	0 (0)	1 (< 1)
Blood and lymphatic system					
Anaemia	Common	15 (5.1)	3 (1.0)	0 (0)	2 (< 1)
Immune system disorders					
Glomerulonephritis	Uncommon	1 (< 1)	1 (< 1)	0 (0)	1 (< 1)
Pneumonitis[2]	Uncommon	1 (< 1)	1 (< 1)	0 (0)	0 (0)
Psoriasis[3]	Uncommon	1 (< 1)	1 (< 1)	0 (0)	0 (0)
Vasculitis	Uncommon	1 (< 1)	0 (0)	0 (0)	0 (0)
Metabolism and nutrition disorders					
Dehydration	Common	12 (4.1)	5 (1.7)	0 (0)	2 (< 1)
Nervous system disorders					
Headache	Very Common	55 (18.8)	2 (< 1)	0 (0)	0 (0)
Dizziness	Common	28 (9.6)	0 (0)	0 (0)	0 (0)
Eye disorders					
Keratitis herpetic	Uncommon	1 (< 1)	0 (0)	0 (0)	0 (0)
Vascular disorders					
Flushing	Common	11 (3.8)	0 (0)	0 (0)	0 (0)
Deep vein thrombosis	Common	6 (2.1)	5 (1.7)	0 (0)	3 (1.0)
Respiratory, thoracic and mediastinal disorders					
Oropharyngeal pain	Common	17 (5.8)	0 (0)	0 (0)	0 (0)
Obstructive airways disorder	Uncommon	1 (< 1)	1 (< 1)	0 (0)	1 (<1)
Gastrointestinal disorders					
Nausea	Very Common	104 (35.6)	1 (< 1)	0 (0)	0 (0)
Vomiting	Very Common	62 (21.2)	5 (1.7)	0 (0)	2 (< 1)
Diarrhoea	Very Common	55 (18.8)	1 (< 1)	0 (0)	0 (0)
Constipation	Very Common	34 (11.6)	0 (0)	0 (0)	2 (< 1)
Abdominal pain	Common	26 (8.9)	3 (1.0)	0 (0)	0 (0)
Abdominal discomfort	Common	6 (2.1)	0 (0)	0 (0)	0 (0)

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Footnotes are defined on next page of the table.

		Imlygic (N = 292)			
			Events with Severity		
System Organ Class Preferred Term	CIOMS Frequency	All Events n (%)	Grade 3-4 n (%)	Grade 5 n (%)	Serious Events n (%)
Skin and subcutaneous tissue					
Rash	Common	26 (8.9)	1 (< 1)	0 (0)	0 (0)
Vitiligo	Common	15 (5.1)	0 (0)	0 (0)	0 (0)
Dermatitis	Common	5 (1.7)	0 (0)	0 (0)	0 (0)
Musculoskeletal and connective tissue disorders					
Myalgia	Very Common	51 (17.5)	1 (< 1)	0 (0)	0 (0)
Arthralgia	Very Common	50 (17.1)	2 (< 1)	0 (0)	0 (0)
Pain in extremity	Very Common	48 (16.4)	4 (1.4)	0 (0)	0 (0)
Groin pain	Common	10 (3.4)	0 (0)	0 (0)	0 (0)
General disorders and administration					
Fatigue	Very Common	147 (50.3)	5 (1.7)	0 (0)	0 (0)
Chills	Very Common	142 (48.6)	0 (0)	0 (0)	1 (< 1)
Pyrexia	Very Common	125 (42.8)	0 (0)	0 (0)	5 (1.7)
Injection site reactions4	Very Common	115 (39.4)	3 (1.0)	0 (0)	0 (0)
Influenza like illness	Very Common	89 (30.5)	2 (< 1)	0 (0)	1 (< 1)
Malaise	Common	12 (4.1)	0 (0)	0 (0)	0 (0)
Axillary pain	Common	10 (3.4)	0 (0)	0 (0)	0 (0)
Investigations					
Weight decreased	Common	17 (5.8)	1 (< 1)	0 (0)	0 (0)
Injury, poisoning and procedural complications					
Contusion	Common	14 (4.8)	0 (0)	0 (0)	0 (0)
Procedural pain	Common	9 (3.1)	1 (< 1)	0 (0)	1 (< 1)
Wound complication	Common	4 (1.4)	0 (0)	0 (0)	0 (0)
Wound secretion	Common	4 (1.4)	0 (0)	0 (0)	0 (0)

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Adverse events were coded using MedDRA version 15.1.
Adverse Reactions were defined as: adverse events with >= 2% more frequent incidence in Imlygic-treated patients compared to GM-CSF-treated patients in Study 1 OR adverse events with less than 2% difference, but with a biologically plausible mechanism and similar in medical concept to other adverse events.
The classification of Very common, Common and Uncommon events is based on cutoff percentages that were applied to adverse event incidence in the "All Events" column of the Imlygic arm.
[1] Plasmacytoma at the injection site.
[2] Pneumonitis is considered an immune mediated event and is therefore categorized with the other adverse events in the system organ class of Immune system disorders.
[3] Worsening psoriasis.
[4] Injection Site Reactions includes Injection site pain, Injection site erythema, Injection site haemorrhage, Injection site swelling, Injection site reaction, Injection site inflammation, Secretion discharge, Injection site discharge, Injection site warmth.

11.3 – Risks, toxicities and adverse drug reactions – Pembrolizumab

Pembrolizumab dosing likely will produce side effects, and not all side effects may be known. Specific identified risks and potential risks are highlighted below, as well as adverse drug reactions observed in clinical trials:
Information extracted from Pembrolizumab Prescribing Information, available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125514lbl.pdf

11.3.1 – Identified risks - Pembrolizumab

Risk: Immune-Mediated Pneumonitis

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

Risk: Immune-Mediated Colitis
Colitis (including microscopic colitis) occurred in 4 (1%) of 411 patients, including Grade 2 or 3 cases in 1 (0.2%) and 2 (0.5%) patients, respectively, receiving pembrolizumab. The median time to onset of colitis was 6.5 months (range 2.3-9.8). The median duration was 2.6 months (range 0.6 weeks-3.6 months). All three patients with Grade 2 or 3 colitis were treated with high-dose corticosteroids (greater than or equal to 40 mg prednisone or equivalent per day) with a median initial dose of 70 mg/day of prednisone or equivalent; the median duration of initial treatment was 7 days (range 4-41), followed by a corticosteroid taper. One patient (0.2%) required permanent discontinuation of pembrolizumab due to colitis. All four patients with colitis experienced complete resolution of the event.

Risk: Immune-Mediated Hepatitis
Hepatitis (including autoimmune hepatitis) occurred in 2 (0.5%) of 411 patients, including a Grade 4 case in 1 (0.2%) patient, receiving pembrolizumab. The time to onset was 22 days for the case of Grade 4 hepatitis which lasted 1.1 months. The patient with Grade 4 hepatitis permanently discontinued pembrolizumab and was treated with high-dose (greater than or equal to 40 mg prednisone or equivalent per day) systemic corticosteroids followed by a corticosteroid taper. Both patients with hepatitis experienced complete resolution of the event.

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

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

Risk: Immune-Mediated Hyperthyroidism and Hypothyroidism
Hyperthyroidism occurred in 5 (1.2%) of 411 patients, including Grade 2 or 3 cases in 2 (0.5%) and 1 (0.2%) patients, respectively, receiving pembrolizumab. The median time to onset was 1.5 months (range 0.5-2.1). The median duration was 2.8 months (range 0.9 to 6.1). One of two patients with Grade 2 and the one patient with Grade 3 hyperthyroidism required initial treatment with high-dose corticosteroids (greater than or equal to 40 mg prednisone or equivalent per day) followed by a corticosteroid taper. One patient (0.2%) required permanent discontinuation of pembrolizumab due to hyperthyroidism. All five patients with hyperthyroidism experienced complete resolution of the event. Hypothyroidism occurred in 34 (8.3%) of 411 patients, including a Grade 3 case in 1 (0.2%) patient, receiving pembrolizumab. The median time to onset of hypothyroidism was 3.5 months (range 0.7 weeks-19 months). All but two of the patients with hypothyroidism were treated with long-term thyroid hormone replacement therapy. The other two patients only required short-term thyroid hormone replacement therapy. No patient received corticosteroids or discontinued pembrolizumab for management of hypothyroidism.

Risk: Infusion reactions

Pembrolizumab infusion reactions may consist of fever, chills/rigor, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticarial, rash, vomiting, myalgia, dizziness, or hypertension. Severe reactions may include acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock. Patients should be closely monitored for such reactions. Guidelines for patients who experience an infusion related or allergic reaction during or after infusion with pembrolizumab are detailed in Appendix B.

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

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

11.3.2 - Adverse Drug Reactions – Pembrolizumab

Adverse drug reactions observed in an uncontrolled, open-label, multiple cohort trial in which 411 patients with unresectable or metastatic melanoma received pembrolizumab at either 2 mg/kg every 3 weeks or 10 mg/kg every 2 or 3 weeks (Trial 1). The median duration of exposure to pembrolizumab was 6.2 months (range 1 day to 24.6 months) with a median of 10 doses (range 1 to 51).

Pembrolizumab was discontinued for adverse reactions in 9% of the 411 patients. Adverse reactions, reported in at least two patients that led to discontinuation of pembrolizumab were:

pneumonitis, renal failure, and pain. Serious adverse reactions occurred in 36% of patients receiving pembrolizumab. The most frequent serious adverse drug reactions reported in 2% or more of patients in Trial 1 were renal failure, dyspnea, pneumonia, and cellulitis. Table 8 presents adverse reactions identified from analyses of the 89 patients with unresectable or metastatic melanoma who received pembrolizumab 2 mg/kg every three weeks in one cohort of Trial 1. This cohort of Trial 1 excluded patients with severe immune-related toxicity related to ipilimumab, defined as any Grade 4 toxicity requiring treatment with corticosteroids or Grade 3 toxicity requiring corticosteroid treatment (greater than 10 mg/day prednisone or equivalent dose) for greater than 12 weeks; a medical condition that required systemic corticosteroids or other immunosuppressive medication; a history of pneumonitis or interstitial lung disease; or any active infection requiring therapy, including HIV or hepatitis B or C. Of the 89 patients in this cohort, the median age was 59 years (range 18-88), 33% were age 65 years or older, 53% were male, 98% were white, 44% had an elevated LDH, 84% had Stage M1c disease, 8% had brain metastases, and 70% received two or more prior therapies for advanced or metastatic disease. The median duration of exposure to pembrolizumab was 6.2 months (range 1 day to 15.3 months) with a median of nine doses (range 1 to 23). Fifty-one percent of patients were exposed to pembrolizumab for greater than 6 months and 21% for greater than 1 year. Pembrolizumab was discontinued for adverse reactions in 6% of the 89 patients. The most common adverse reactions (reported in at least 20% of patients) were fatigue, cough, nausea, pruritus, rash, decreased appetite, constipation, arthralgia, and diarrhea.

Table 8: Adverse Reactions in ≥10% of patients with unresectable or metastatic melanoma treated with pembrolizumab 2mg/kg every 3 weeks.

Adverse Reaction	All Grades (%)	Grade 3* (%)
General Disorders and Administration Site Conditions		
Fatigue	47	7
Peripheral Edema	17	1
Chills	14	0
Pyrexia	11	0
Gastrointestinal Disorders		
Nausea	30	0
Constipation	21	0
Diarrhea	20	0
Vomiting	16	0
Abdominal pain	12	0
Respiratory, Thoracic And Mediastinal Disorders		
Cough	30	1
Dyspnea	18	2
Skin And Subcutaneous Tissue Disorders		
Pruritus	30	0
Rash	29	0
Vitiligo	11	0
Metabolism and Nutrition Disorders		
Decreased appetite	26	0
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	20	0
Pain in extremity	18	1
Myalgia	14	1
Back pain	12	1
Nervous System Disorders		
Headache	16	0
Dizziness	11	0
Blood and Lymphatic System Disorders		
Anemia	14	5
Psychiatric Disorders		

Insomnia	14	0
Infections and Infestations		
Upper respiratory tract infection	11	1

There were no Grade 5 adverse reactions reported. Of the ≥10% adverse reactions, none was reported as Grade 4.

Other clinically important adverse reactions observed in up to 10% of patients treated with pembrolizumab were: *Infections and infestations:* sepsis

Table 9: Laboratory Abnormalities Increased from baseline in ≥20% of patients with unresectable or metastatic melanoma treated with pembrolizumab 2mg/kg every 3 weeks.

Laboratory Test	All Grades %	Grades 3-4 %
Chemistry		
Hyperglycemia	40	2*
Hyponatremia	35	9
Hypoalbuminemia	34	0
Hypertriglyceridemia	25	0
Increased Aspartate Aminotransferase	24	2*
Hypocalcemia	24	1
Hematology		
Anemia	55	8*

* Grade 4 abnormalities in this table limited to hyperglycemia, increased aspartate aminotransferase, and anemia (one patient each)

11.4 Dose adjustments, delays, rules for withholding and restarting treatment and permanent discontinuation.

11.4.1 Talimogene laherparepvec

Dose reductions – talimogene laherparepvec

Dose reductions with regards to changes in the concentrations of talimogene laherparepvec are not permitted. However, patients may require a reduction in the volume injected due to a disease response (defined in dosing section) or due to local toxicity at the injection site.

Dose delays and rules for withholding/restarting treatment – talimogene laherparepvec

If a subject experiences any of the following treatment-related toxicities, talimogene laherparepvec administration should be delayed until the toxicity has resolved to at least CTCAE grade 1 or baseline:

- grade 2 or greater immune-mediated adverse events, with the exception of vitiligo
- grade 2 or greater allergic reactions
- any other grade 3 or greater hematologic or non-hematologic toxicity

Upon restarting study therapy, the patient's treatment schedule should be reset from the date that therapy is reinitiated as to maintain appropriate treatment windows between therapy administrations.

If the subject requires corticosteroid dosing of >10 mg prednisone daily (or equivalent) and/or other immunosuppressive medication for related toxicities talimogene laherparepvec dosing must be held until the corticosteroid dose has decreased to ≤10 mg prednisone daily (or equivalent) and the administration of the other immunosuppressive medication has discontinued.

Subjects who are receiving talimogene laherparepvec may not receive systemic intravenous or oral antiherpetic drugs (e.g., acyclovir, valacyclovir, famciclovir), but may receive a topically administered antiherpetic drug more than 20 cm from a talimogene laherparepvec injection site. Dosing should be permanently discontinued if, in the opinion of the investigator, the subject develops clinical evidence of any systemic herpes infection (such as encephalitis or disseminated infection).

Dosing of talimogene laherparepvec could also be delayed for active herpetic cutaneous or mucosal lesions, herpes labialis, antiviral therapy, or active dermatoses in the region of the injected tumors.

Permanent discontinuation – talimogene laherparepvec

If talimogene laherparepvec dosing is delayed by more than 9 weeks from the last dose (approximately 12 weeks from the previous dose) due to the occurrence of adverse events that are related to talimogene laherparepvec, then treatment should be discontinued. If talimogene laherparepvec dosing is delayed by more than 9 weeks approximately 12 weeks from the previous dose) for reasons other than treatment-related toxicity, the case must be reviewed by the principal investigator to determine if the subject can resume talimogene laherparepvec therapy.

Treatment with talimogene laherparepvec should be suspended if systemic intravenous or oral acyclovir or other anti-viral therapy is required; if ongoing treatment is required then treatment should be permanently discontinued.

In addition to criteria outlined in section 9.2, talimogene laherparepvec is to be permanently discontinued for subjects meeting any of the following criteria:

- A grade 2 or greater immune-mediated adverse event (with the exception of vitiligo) or allergic reactions attributed to talimogene laherparepvec that would require a dose delay of greater than 9 weeks from the date of the planned dose (i.e., approximately 12 weeks from the previous dose)

  NOTE: immune-mediated glomerulonephritis, vasculitis, and pneumonitis and exacerbation of psoriasis have been observed in subjects receiving talimogene laherparepvec in clinical trials. Most of these subjects had a history of other autoimmune disease and/or prior treatment with agents that offered plausible

alternative etiologies; however, immune-mediated adverse events can potentially involve any organ system.

- Plasmacytoma has been observed with the administration of talimogene laherparepvec. Permanently discontinue talimogene laherparepvec if development of a plasmacytoma is observed.
- Any talimogene laherparepvec-related non-hematologic or hematologic toxicities Grade 3 or greater that, in the opinion of the investigator, would require a dose delay of greater than 9 weeks (approximately 12 weeks from the previous dose) or discontinuation of therapy.
- A female subject becomes pregnant or fails to use 2 highly effective methods of contraception (for those subjects who are able to conceive).
- A female subject breast feeds while on study treatment.
- The subject develops clinical evidence of any systemic herpes infection (such as encephalitis or disseminated infection).
- In the event talimogene laherparepvec is delayed or permanently discontinued for talimogene laherparepvec-related toxicity, pembrolizumab may continue to be administered, as long as the toxicity is clearly not related to pembrolizumab. Likewise in the event pembrolizumab is delayed or permanently discontinued for pembrolizumab-related toxicity, talimogene laherparepvec may continue to be administered, as long as the toxicity is clearly not related to talimogene laherparepvec.

11.4.2 Pembrolizumab

Dose reductions – Pembrolizumab

Dose reductions of pembrolizumab are not permitted.

Dose Modification and Toxicity Management

Adverse events (both non-serious and serious) associated with pembrolizumab exposure, including coadministration with additional compounds, may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of pembrolizumab/combination treatment and may affect more than one body system simultaneously. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per table 10 below. See Section 5.6 for supportive care guidelines, including use of corticosteroids.

Attribution of Toxicity:
When study interventions are administered in combination, attribution of an adverse event to a single component is likely to be difficult. Therefore, while the investigator may attribute

a toxicity event to the combination, to talimogene laherparepvec alone or to pembrolizumab alone], for adverse events listed in Table 10, both interventions must be held according to the criteria in Table 10 Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events Associated with Pembrolizumab.

Holding Study Interventions:
When study interventions are administered in combination, if the AE is considered immune-related, both interventions should be held according to recommended dose modifications.

Restarting Study Interventions:
Participants may not have any dose modifications (no change in dose or schedule) of pembrolizumab in this study, as described in Table 10.

- If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from all study interventions.
- If the toxicities do resolve and conditions are aligned with what is defined in Table 10, the combination of talimogene laherparepvec and pembrolizumab may be restarted at the discretion of the investigator.[In these cases where the toxicity is attributed to the combination or to talimogene laherparepvec alone, re-initiation of pembrolizumab as a monotherapy may be considered at the principal investigator's discretion

Table 10. Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab monotherapy and IO combinations

General instructions:
1. **Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.**
2. **For situations where study intervention has been withheld, study intervention can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Study intervention should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks.**
3. **For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.**

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor subjects for signs and symptoms of pneumonitis • Evaluate subjects with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Grade 3 or 4, or recurrent grade 2	Permanently discontinue		
Diarrhea / colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2mg/kg prednisone or equivalent) followed by taper	• Monitor subjects for signs and symptoms of enterocolitis (i.e. diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e. peritoneal signs and ileus). • Subjects with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis.

	Recurrent Grade 3 or Grade 4	Permanently discontinue		• Subjects 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.
AST / ALT elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5-1mg/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 1-2mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• Initiate insulin replacement therapy for subjects with T1DM • Administer anti-hyperglycemic in subjects with hyperglycemia	• Monitor subjects 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 (e.g. propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or Permanently discontinue[d]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (e.g. 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- to 2mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 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		
Myocarditis	Grade 1	Withhold		• Ensure adequate evaluation to confirm etiology and/or exclude other causes

	Grade 2, 3, or 4	Permanently discontinue	• Based on severity of AE administer corticosteroids	
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All Other immune-related AEs	Grade 3, or intolerable/ persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 4 or recurrent Grade 3	Permanently discontinue		

NOTES:

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] AST/ALT: >3.0 to5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 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: encephalitis and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

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). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the principal investigator. The reason for interruption should be documented in the patient's study record. The patient's treatment schedule should be reset from the date that therapy is reinitiated.

11.5 Guidelines for the management of specific and immune-related toxicities

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

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

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

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

  Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).
    - All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
    - For **Grade 2 diarrhea/colitis,** administer oral corticosteroids.
    - For **Grade 3 or 4 diarrhea/colitis,** treat with intravenous steroids followed by high dose oral steroids.
    - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**
    - For **T1DM** or **Grade 3-4** Hyperglycemia
        - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
        - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.
- **Hypophysitis**:
    - For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
    - For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hyperthyroidism or Hypothyroidism**:

  Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.
  - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
    - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care.
  - **Grade 3-4** hyperthyroidism
    - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- **Hepatic**:
  - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with IV or oral corticosteroids
  - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
  - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.
- **Renal Failure or Nephritis**:
  - For **Grade 2** events, treat with corticosteroids.
  - For **Grade 3-4** events, treat with systemic corticosteroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- **Management of Infusion Reactions**: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Table 11 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 11: Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Subject is permanently discontinued from further study drug treatment.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

11.6 AE and SAE reporting

11.6.1 Time Period and Frequency of Detecting AEs and SAEs

The investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE. See section below for the timeline for reporting SAEs.

AEs and SAEs will be collected from the time the first dose of study treatment is administered until 30 days (+7 days) following discontinuation of study treatment regardless of initiation of a new cancer therapy or transfer to hospice.

After discontinuation of study treatment, the investigator will monitor all AEs/SAEs that are ongoing until resolution or stabilization of the event or until the subject is lost to follow-up. At any time after treatment discontinuation the investigator may report any adverse event that they believe possibly related to study treatment.

11.6.2 Prompt Reporting of Serious Adverse Events and Other Events to MSKCC IRB

Please see section 17.2 for SAE reporting guidelines.

11.6.3 CTCAE term (AE description) and grade

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.03. A copy of the CTCAE version 4.03 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

11.6.4 Attribution of the AE:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment.
- Possible – The AE may be related to the study treatment.
- Unlikely – The AE is doubtfully related to the study treatment.
- Unrelated – The AE is clearly NOT related to the study treatment.

11.7 Pregnancy Testing, Prevention and Lactation Reporting

11.7.1 Pregnancy Testing and Prevention

Talimogene laherparepvec is not considered to be teratogenic. Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm.

For this trial, male subjects will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

The need for a screening pregnancy test depends on whether a female subject is of childbearing potential or non-childbearing potential.

Female subjects will be considered of non-reproductive potential if they are either:

(1) Postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

OR

(2) Have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;

OR

(3) Has a congenital or acquired condition that prevents childbearing.

A female of child-bearing potential is defined as any female who does not meet the criteria of non-childbearing potential as described in the previous paragraph.
If a female subject is of childbearing potential, she must have a serum β-HCG pregnancy test at screening and performed within 72 hours of the first dose of study treatment. Subjects with positive pregnancy test result must be excluded from the study.
Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 90 days after the last dose of talimogene laherparepvec and 120 days after the last dose of pembrolizumab by complying with one of the following:
(1) Practice abstinence† from sexual activity;
OR
(2) Use (or have their partner use) acceptable contraception during sexual activity.
Acceptable methods of contraception during study treatment and up to 30 days following the final dose of talimogene laherparepvec include:
Male and female latex condoms
Acceptable methods of contraception during study treatment from 30 days after the final dose of talimogene laherparepvec include:
Single method (one of the following is acceptable):

- intrauterine device (IUD)
- vasectomy of a female subject's male partner
- contraceptive rod implanted into the skin

Combination method (requires use of two of the following):

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection
- Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.
- If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120

days after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.
If a female subject is suspected to be pregnant during the study, a serum pregnancy test must be performed. If pregnancy is confirmed, subject must stop study treatment immediately and the pregnancy must be reported. A report confirming a female subject to be pregnant or lactating has to be reported to Amgen and Merck within 24 hours of site awareness and submitted within 10 days of sponsor awareness. The site will contact the pregnant subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to Merck and Amgen without delay and within 2 working days to Merck and Amgen if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).
The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn per MSKCC guidelines. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to Merck and Amgen and followed in the same manner as a pregnant female subject outlined in the previous paragraph.

11.8 Additional Information Related to Pembrolizumab and Reporting

11.8.1 Definition of a Pembrolizumab Overdose for This Protocol and Reporting of Pembrolizumab Overdose to Merck

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. Appropriate supportive treatment should be provided if clinically indicated. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.
If an adverse event(s) is associated with ("results from") the overdose of a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.
If a dose of Merck's product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."
All reports of overdose with and without an adverse event must be reported per MSKCC guidelines and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

11.8.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported per MSKCC guidelines and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220).
For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported per MSKCC guidelines and within 2 working days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified

intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Merck product, must be reported within 24 hours to Merck Global Safety.

Events of clinical interest for this trial include:
1. an overdose of Merck product, as defined in Section 11.8.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.
2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

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

11.9 Additional Information Related to Accidental Exposure to Talimogene Laherparepvec

In order to better assess and understand the potential risks to treated patients and/or third parties following the treatment of clinical trial subjects with talimogene laherparepvec, special reporting procedures apply for accidental exposures to talimogene laherparepvec and for suspected herpetic events. See Table 12 for a summary of reporting requirements.

11.9.1 Accidental Occupational Exposure of HCPs to Talimogene Laherparepvec

HCPs involved in your clinical trial who were directly exposed to talimogene laherparepvec (e.g., needle stick, splash back) but who are without signs or symptoms of herpetic illness should be reported to Amgen at 1-855-IMLYGIC (1-855-465-9442).

1.9.2 Suspected Herpetic Events

Suspected herpetic events must be reported to Amgen within 24 hours of awareness. Reporting is required for: (1) suspected herpetic events in treated patients; (2) suspected herpetic events in at risk HCPs with direct or indirect exposure and 3) suspected herpetic events in treated patient's close contacts, as outlined in Table 12. An example of the Suspected IMLYGICTM (Talimogene laherparepvec) or Herpes Virus Associated Adverse Event can be found in Appendix C.

In addition to reporting these events, suspected herpetic lesions should be swabbed and submitted for qPCR testing for the detection of talimogene laherparepvec. Samples should be collected using appropriate technique and a flocked swab from site supplies. This test is likely to be more reliable if performed within the first three days of symptom appearance, however, all lesions should be swabbed, regardless of the timing of presentation. Amgen does not require qPCR or other testing for wild type HSV-1.

Reporting Process for ISS Treated Patients:

Any suspected herpetic lesion should be reported to Amgen at 1-855- IMLYGIC (1-855-465-9442), evaluated by the Sponsor/Investigator and swabbed for qPCR testing.

Once an initial report has been made, additional materials will be provided, including reporting forms and supplies needed for shipment of swab samples. Amgen will require patient consent for qPCR testing, which must be obtained prior to swabbing.

Reporting Process for HCPs and Close Contacts:

Sponsor/Investigator should advise any HCPs and/or Close Contacts with suspected herpetic lesions to contact their personal physician to facilitate reporting to Amgen. Suspected herpetic lesions can be reported by the Sponsor / Investigator, personal physician or exposed individual to Amgen at 1-855-IMLYGIC (1-855-465-9442). Once an initial report has been made, additional materials will be provided, including reporting forms and supplies needed for the shipment of swab samples. Amgen will require patient consent for qPCR testing, which must be obtained prior to swabbing

Table 12. Accidental Exposure & Herpetic Event Reporting Requirement Summary

Exposed person	Reporter	Timeframe for reporting to Amgen	Report mechanism	Timing of Swab Collection	qPCR testing Required?	Responsible person 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) to report event	Collect swabs from suspected lesions (ideally within 3 days of appearance of symptoms)	Yes, if consent obtained	Investigator	Investigator and Amgen
HCP directly exposed to product (e.g., needle stick, splash back) without signs of symptoms of herpetic illness	HCP's personal physician or impacted person	Within 24 hours of reporters 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 reporters awareness	Contact Amgen at 1-855-IMLYGIC (1-855-465-9442) to report event	Collect swabs from suspected lesions (ideally within 3 days of appearance	Yes, if consent obtained	HCP or HCP's personal physician	HCP's personal physician and Amgen

				of symptoms)			
Close Contact (eg caregiver, spouse, child) with suspected herpetic lesions	Investigator , Close Contact's Personal Physician or Close Contact	Within 24 hours of reporters awareness	Contact Amgen at 1-855-IMLYGIC (1-855-465-9442) to report event	Collect swabs from suspected lesions (ideally within 3 days of appearanc e of symptoms)	Yes, if consent obtained	Investigator, Close Contact's Personal Physician	Close Contact's personal physician and Amgen

11.9.3 Accidental Spills

Accidental spills of talimogene laherparepvec should be managed as per local institutional guidelines. All disposable materials contaminated with talimogene laherparepvec must be destroyed and disposed of in compliance with local institutional guidelines.

11.9.4 Infections

Tumor necrosis may be seen with the use of talimogene laherparepvec. The presence of necrotic or ulcerating lesions may pre-dispose the subject 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.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

12.1 Antitumor effect

All patients will undergo a baseline staging CT scan of the chest (with or without contrast), abdomen and pelvis (with contrast if renal function permits), and MRI abdomen/pelvis (with and without contrast) if deemed necessary by the treating physician. Response evaluations will occur at week 8 and every 8 weeks subsequently (± 1 week window) until 12 months, and then less frequently at the discretion of the treating investigator.

Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline, version 1.1 (Primary response criteria).[88] Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

In addition, patients will also be evaluated using the Immune-related revised Response Evaluation Criteria in Solid Tumors (irRECIST), [89] which ***will not be used*** for treatment decisions (Secondary Response Criteria) and are discussed separately in section 12.12.

In subjects who have initial evidence of progressive disease (PD) as per RECIST criteria or irRECIST criteria, it is at the discretion of the investigator to continue a subject on study treatment until confirmation of PD ≥ 4 weeks. This clinical judgment decision should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data.

Subjects will receive treatment if they are clinically stable as defined by the following criteria:

- Absence of signs and symptoms indicating PD.
- No decline in the Eastern Cooperative Oncology Group (ECOG) performance status
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention

12.2 Definitions

Evaluable for toxicity – All patients will be evaluable for toxicity from the time of their first treatment with talimogene laherparepvec and/or pembrolizumab.
Evaluable for efficacy – Only those patients who have a measurable disease based on RECIST 1.1 criteria will be eligible for this study, as highlighted in Section 6.0. These patients will have their response classified according to the definitions stated below.
Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable. Note: one cycle of therapy consists of 21 days where the study therapy (TVEC and pembrolizumab) is administered at the start of the cycle on day 1)

12.2.1 Disease Parameters

Measurable disease – Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as >20mm by chest x-ray, as >10mm with CT scan or MRI, or >10mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

To be considered pathologically enlarged and measurable, a lymph node must be > 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Note: Tumor lesions that are situated in a previously irradiated area are not considered measurable unless there is evidence of progression after radiation therapy.

Non-measurable disease – All other lesions (or sites of disease), including small lesions (longest diameter <10mm or pathological lymph nodes with ≥10 to <15mm 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 as non-measurable.
Target lesions – All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as a reference to further characterize any objective regression in the measurable dimension of the disease.

Non-target lesions – All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence or in rare cases unequivocal progression of each should be noted throughout follow-up.

12.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up portion of study. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions - Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules).

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

Conventional CT and MRI - This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, 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 be performed with breath-hold scanning techniques, if possible.

12.3.1 Primary Response Criteria (RECIST 1.1)

12.3.1.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

12.3.1.2 Evaluation of Non-Target Lesions

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

Non-CR/Non-PD: Persistence of one or more non-target lesion(s).

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or MSKCC Principal Investigator).

12.3.1.3 Evaluation of Best Response

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

Table 13. Evaluation of Best Response – RECIST criteria

Target Lesions	Non-Target Lesions	New Lesions	Best Response	Best Response for This Category also Requires:
CR	CR	No	CR	≥ 4 wks. Confirmation
CR	Non-CR/ Non-PD	No	PR	≥ 4 wks. Confirmation
PR	Non-CR/ Non-PD	No	PR	
SD	Non-CR/ Non-PD	No	SD	documented at least once ≥ 4 wks. from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

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

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

12.4 Confirmation of response

Complete or partial response may only be claimed if the criteria for each are met at a subsequent time point (≥4 weeks later) in studies with a primary endpoint that include response rate.

12.4.1 Special note on target lesions that become "too small to measure"

While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2mm). However, sometimes, lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure". When this occurs, it is important that a value be recorded on the D2M form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned.

12.5 Not evaluable (NE)

When no imaging/measurement is done at all at a particular time point, the patient is considered not evaluable (NE) at that time point.

12.6 Early death

If the patient has no repeat tumor assessments following initiation of study therapy resulting from the death of the patient due to disease or treatment, it is considered early death.

12.7 Symptomatic Deterioration

Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time be recorded as “symptomatic deterioration”. Every effort should be made to document objective progression even after discontinuation of treatment.

12.8 Duration of response

Defined as the time measurement criteria are first met for CR/PR until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurement recorded on study).

12.9 Duration of stable disease

Measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

12.10 Progression-Free Survival (PFS)

PFS is defined as the period from start of study treatment until recurrent or progressive of disease (POD) is objectively documented (taking as reference for progressive disease the smallest measurement recorded on study), death, or date of last evaluable tumor assessment

12.11 Overall Survival (OS)

OS is defined as the observed length of life from start of study treatment to death or the date of last contact.

12.12 Secondary Response Criteria – Modified immune-related response evaluation Criteria in Solid (irRECIST)

Immune related RECIST (irRECIST)
In 2013, Nishino et al. demonstrated that immune-related response criteria using unidimensional measurements were highly concordant with the bidimensional results of irRC, but with less measurement variability. Based on these findings and in order to utilize

both the established criteria of irRC and RECIST 1.1, the two systems have been adapted, modified, and combined into the Immune-related Response Evaluation Criteria in Solid Tumors (irRECIST). The adapted irRECIST criteria are modifications to the irRC, incorporating the findings of Nishino et al. and the advantages of RECIST 1.1 while overcoming the shortcomings of each of the other guidelines.

irRECIST
Immune-related RECIST (irRECIST) guidelines according to Bohnsack et al. are presented below.

I. Baseline Assessments in irRECIST

In irRECIST, baseline assessment and measurement of measurable/non-measurable and target/non-target lesions and lymph nodes are in line with RECIST 1.1.

One new definition is added: If a subject has no measurable and no non-measurable disease at baseline the radiologist will assign 'No Disease' (irND) as the overall tumor assessment for any available follow-up time points unless new measurable lesions are identified and contribute to the total measured tumor burden (TMTB). irND is a valid assessment in studies with adjuvant setting where the protocol and study design allow the inclusion of subjects with no visible disease

Follow-up Assessments in irRECIST

A. Follow-up recording of target and new measurable lesions

The key difference in irRECIST is that the appearance of new lesions does not automatically indicate progression. Instead, all measured lesions (baseline-selected target lesions and new measurable lesions) are combined into the total measured tumor burden (TMTB) at follow up. Baseline-selected target lesions and new measurable lesions are NOT assessed separately. Measurements of those lesions are combined into the TMTB, and one combined assessment provided.

In order to be selected as new measurable lesions (≤ 2 lesions per organ, ≤ 5 lesions total, per time point), new lesions must meet criteria as defined for baseline target lesion selection and meet the same minimum size requirements of 10 mm in long diameter and minimum 15 mm in short axis for new measurable lymph nodes. New measurable lesions should be prioritized according to size, and the largest lesions elected as new measured lesions.

B. Follow-up non-target assessment

RECIST 1.1 definitions for assessment of non-target lesions apply. The response of non-target lesions primarily contributes to the overall response assessments of irCR and irNon-CR/Non-PD (irNN). Non-target lesions do not affect irPR and irSD assessments. Only a massive and unequivocal worsening of non-target lesions alone, even without progress in the TMTB is indicative of irPD. In alignment with RECIST 1.1, baseline selected non-target lesions can never convert to measurable lesions, not even if they increase in size at

subsequent time points and become measurable. Only true new lesions can be measured and contribute to the TMTB.

C. Follow-up for New Non-Measurable Lesions

All new lesions not selected as new measurable lesions are considered new non-measurable lesions and are followed qualitatively. Only a massive and unequivocal progression of new non-measurable lesions leads to an overall assessment of irPD for the time point. Persisting new non-measurable lesions prevent irCR.

Overall Assessments for irRECIST

The irRECIST overall tumor assessment is based on TMTB of measured target and new lesions, non-target lesion assessment and new non-measurable lesions.

At baseline, the sum of the longest diameters (SumD) of all target lesions (up to 2 lesions per organ, up to total 5 lesions) is measured. At each subsequent tumor assessment (TA), the SumD At each subsequent tumor assessment (TA), the SumD of the target lesions and of new, measurable lesions (up to 2 new lesions per organ, total 5 new lesions) are added together to provide the total measurable tumor burden (TMTB).

Table 14. Evaluation of Overall Assessment – irRECIST criteria

Overall Assessments by irRECIST	
Complete Response (irCR)	Complete disappearance of all measurable and non-measurable lesions. Lymph nodes must decrease to < 10 mm in short axis.
Partial Response (irPR)	Decrease of ≥ 30% in TMTB relative to baseline, non-target lesions are irNN, and no unequivocal progression of new non-measurable lesions • If new measurable lesions appear in subjects with **no target lesions at baseline**, irPD will be assessed. That irPD time point will be considered a new baseline, and all subsequent time points will be compared to it for response assessment. irPR is possible if the TMTB of new measurable lesions decreases by ≥ 30% compared to the first irPD documentation • irRECIST can be used in the **adjuvant setting**, in subjects with no visible disease on CT/MRI scans. The appearance of new measurable lesion(s) automatically leads to an increase in TMTB by 100% and leads to irPD. These subjects can achieve a response if the TMTB decreases at

	follow-up, as a sign of delayed response. • Based on the above, sponsors may consider enrolling subjects with no measurable disease and/or no visible disease in studies with response related endpoints.
Stable Disease (irSD)	Failure to meet criteria for irCR or irPR in the absence of irPD
Progressive Disease (irPD)	Minimum 20% increase and minimum 5 mm absolute increase in TMTB compared to nadir, or irPD for non-target or new non-measurable lesions. Confirmation of progression is recommended minimum 4 weeks after the first irPD assessment. An irPD confirmation scan may be recommended for subjects with a minimal TMTB %-increase over 20% and especially during the flare time-window of the first 12 weeks of treatment, depending on the compound efficacy expectations, to account for expected delayed response. • In irRECIST a substantial and unequivocal increase of **non-target lesions** is indicative of progression. • IrPD may be assigned for a subject with multiple **new non-measurable lesions** if they are considered to be a sign of unequivocal massive worsening
Other	**irNE:** used in exceptional cases where insufficient data exist. **irND:** in adjuvant setting when no disease is detected **irNN:**, no target disease was identified at baseline, and at follow-up the subject fails to meet criteria for irCR or irPD

12.13.17 Verification of Response

irRECIST response must be confirmed no less than 4 weeks from the initial irRECIST documented response.

13.0 CRITERIA FOR REMOVAL FROM STUDY

Patients will be removed from the study when any of the criteria listed below applies. The reason for removal from the study and the date the patient was removed must be documented in the EDC system.

Patients may be replaced if they come off study for reasons other than progressive disease prior to receiving their second dose of talimogene laherparepvec and/or pembrolizumab. Unless otherwise stated, patients will be included in the safety and/or efficacy analyses. Patients evaluable for efficacy analysis will include all patients treated with talimogene

laherparepvec or pembrolizumab and assessable for response. Patients who are missing an assessment of response post baseline will not be considered evaluable for response unless they missed the assessment due to progression of disease in which case they will be considered non-responders for that time point. Patients who miss an assessment of response post baseline for any reason other than progression of disease will be replaced.

In the absence of treatment delays due to adverse events, treatment with intralesional talimogene laherparepvec may continue until one of the following criteria applies:

- Disappearance of injectable lesions,
- Complete response,
- Confirmed progression of disease or clinical progression,
- Intercurrent illness that prevents further administration of treatment,
- Intolerance of study treatment,
- 35 cycles from the date of the first dose of talimogene laherparepvec and Pembrolizumab in the setting of patients with locally advanced/metastatic sarcoma. Study therapy may continue beyond 35 cycles in patients who are agreeable, deemed to be clinically benefiting from study therapy and at the discretion of the investigator. Patients who discontinue study therapy after a maximum of 35 cycles of study therapy will be allowed to resume study therapy in the setting of progression of disease off study therapy.
- After completion of up to 8 cycles of study therapy in the setting of patients with operable, recurrent sarcoma who will then proceed to surgical resection of their disease

- Patient decides to withdraw from the study
- End of study, whichever occurs first.
- Physician’s decision to withdraw a patient from the study for a reason not listed
- Subject is lost to follow-up

In the absence of treatment delays due to adverse events, treatment with pembrolizumab may continue until one of the following criteria applies:

- Confirmed progression of disease or clinical progression
- Intercurrent illness that prevents further administration of treatment
- Intolerance of study treatmentCompletion of 35 treatments (approximately 2 years) with pembrolizumab
    - Note: The number of treatments is calculated starting with the first dose. Participants who stop the combination or pembrolizumab after receiving 35 doses may be eligible for retreatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 9.2.1. Participants may be retreated in the Second Course Phase (Retreatment) for up to an additional 17 cycles (approximately 1 year).

- After completion of up to eight (8) cycles of study therapy in the setting of patients with recurrent, operablesarcoma who will then proceed to surgical resection of their disease.

- On completion of surgery, these patients will be expected to complete up to 17 treatments (approximately 1 year) total (neoadjuvant and adjuvant) with pembrolizumab as tolerated -

- Patient decides to withdraw from the study,
- End of study, whichever occurs first,
- Physician's decision to withdraw a patient from the study for a reason not listed
- Subject is lost to follow-up

Subjects with a CR may stop injections of talimogene laherparepvec upon complete disappearance of injectable lesions, but treatment with pembrolizumab will be continued unless one of the criteria for treatment discontinuation is met. Study therapy may continue for a total of 35 cycles in the absence of confirmed progression of disease or clinical progression, disappearance of injectable lesions (talimogene laherparepvec only), intercurrent illness that prevents further administration of treatment, or intolerance of study treatment. Patients who discontinue study therapy after a maximum of 35 cycles of study therapy will be allowed to resume study therapy for an additional 17 cycles in the setting of progression of disease off study therapy. In the neoadjuvant setting, TVEC and pembrolizumab will continue for up to 8 cycles prior to surgical resection. On completion of surgery pembrolizumab alone will continue as tolerated for a total of 17 cycles (neoadjuvant and adjuvant therapy).
Due to the mechanism of action, subjects may experience growth in existing tumors or the appearance of new tumors prior to maximal clinical benefit of talimogene laherparepvec and pembrolizumab. The patient may be allowed to continue study treatment after initial RECIST 1.1 defined progression if they are assessed by the treating physician to be deriving clinical benefit and tolerating study treatment. The treating physician may consult with the overall study PI for help with assessing the patient. Such patients should discontinue study therapy upon further evidence of progression.

Safety follows up and End of Study visit
Upon permanent discontinuation from the study treatment for any reason, the following procedures will be performed approximately 30 (+7) days after the last dose of talimogene laherparepvec or the last dose of pembrolizumab, whichever is later in patients with metastatic or locally advanced sarcoma.

- Full medical history, physical exam, assessment of performance status by KPS or ECOG status
- Review of concomitant medications
- Complete vital signs (pulse, blood pressure, temperature, respiratory rate) as well as weight and height. Height may be documented at any time prior to registration.
- 12-lead electrocardiogram (EKG)
- Serum β-HCG pregnancy test for women with child-bearing potential. Complete blood count with differential, including lymphocyte and eosinophil count.

- Comprehensive metabolic panel (glucose, blood urea nitrogen, creatinine, sodium, potassium, chloride, bicarbonate, calcium, total protein, albumin, serum bilirubin, alkaline phosphatase, ASL, AST, phosphorus, magnesium, TSH, T4 free).
- Amylase and lipase
- An optional biopsy will be offered at progression of disease.

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value must be followed until resolution or stabilization of the event.

Reporting of adverse events will occur for up to 30 days for serious adverse events (within 30 [+7] days after the last administration of talimogene laherparepvec or pembrolizumab, whichever is later), Events of Clinical Interest (within 30 [+7] days after the last administration of talimogene laherparepvec or pembrolizumab, whichever is later), and documentation of concomitant medications. In the neoadjuvant cohort, reporting of serious adverse events will occur for up to 30 days from the date of surgical resection.

Long-Term Follow-up Procedures:

All subjects who permanently discontinue study drug for any reason other than withdrawal of full consent will be contacted by clinic visit or telephone to assess survival and initiation of additional sarcoma therapy. Contact for all subjects will be attempted every 12 weeks (± 14 days) following the safety follow-up visit until death, subject withdraws full consent, or up to 12 months after the end of treatment for patients with metastatic or locally advanced sarcoma and for up to 36 months after the completion of surgery for recurrent, operable sarcoma. If patients do not proceed to surgical resection upon conclusion of study therapy, patients will be followed with interval scanning and clinical surveillance every 6-8 weeks for one year or until completion of participation on study.

14.0 BIOSTATISTICS

14.1 Primary and Secondary Endpoints Statistical Considerations

The primary objective is to evaluate the efficacy, as assessed by the best objective response rate (complete response + partial response) at 24 weeks by RECIST 1.1 (primary endpoint; Phase II).The study will use a one stage design based on the exact binomial test. A 5% response rate will be considered not promising;[94,95] a 30% response rate will be considered promising.There will be a maximum accrual of 20 patients to this study, with early stopping rules for predefined treatment-related toxicities. . It will be concluded that the true response rate is > 5% if there are 3 or more patients with an objective response among 20 patients. The design has a type I error rate of 0.08 and a type II error rate of 0.04. This design provides 96% probability of a positive result if the true response rate is at least 30%, and a 92% probability of a negative result if the true response rate is 5% or lower.

The patient population in this study represents patients with locally advanced/metastatic sarcoma that have received at least one line of previous therapy. The references supporting the 5% null rate include the PALETTE, double-blind, randomized placebo-controlled trial[94] and a study looking at the efficacy of eribulin in patients with advanced

sarcoma.[95] The PALETTE study compared pazopanib with placebo in patients with least one regimen containing an anthracycline and a maximum of four previous lines of systemic therapy for metastatic disease (no more than two lines of combination regimens). The response rate for pazopanib was 6% in this study. Pazopanib was granted FDA approval for advanced sarcoma patients that have previously received chemotherapy on the basis of this study which showed an improvement in PFS favoring pazopanib. The second reference refers to a randomized phase 3 study that compared eribulin with dacarbazine in patients with advanced leiomyosarcoma and liposarcoma that have progressed on two previous lines of therapy including an anthracycline. In this study the proportion of patients who had an objective response did not differ between treatment groups (nine [4%] in the eribulin group *vs* 11 [5%] in the dacarbazine group;p=0・62). Dacarbazine is FDA approved for advanced sarcoma and eribulin obtained FDA approval for use in advanced liposarcoma on the basis of this study. Hence, a 5% response rate has been seen with standard chemotherapy agents approved in this patient population. Therefore, in assessing the efficacy of a new therapy in this study population a response rate of > 5% would be preferred to determine the therapy as having a signal of efficacy.

Secondary endpoints include:

1. Feasibility of the combination of talimogene laherparepvec and pembrolizumab in patients with locally advanced or metastatic sarcoma and early-stopping rules

In order to account for unexpected toxicity of the treatment, we will implement an early stopping rule for sequential toxicity monitoring. The results of the previous phase I trial that examined the safety of this combination of drugs reported that all 21 patients in the study experienced a treatment-related adverse event. The treatment related adverse event rate was 19%; G3 treatment related adverse event rate was 29%, there were no G4 treatment related adverse events. However, the rate discontinuation of study therapy due to treatment related adverse events in the phase I study was 0%.[91] This phase II study will be deemed feasible if the primary objective of efficacy of the combination therapy is determined without crossing a boundary that requires early stopping.

The number of patients who experience pre-specified treatment-related toxicity events detailed as per section 11.1.1, that result in the discontinuation of the study drug(s) or delay of their administration ≥ 9 weeks from the planned date of study drug(s) administration , will be recorded. Early stopping rules will be defined such that a 10% rate of occurrence of the above drug-related toxicities is acceptable, whereas a 30% rate would be unacceptable. The study will be continuously monitored for drug-related toxicity events that result in the discontinuation of the study drug(s) or delay of their administration ≥ 9 weeks from the planned date of study drug(s) administration. Early stopping rules are defined as observing such events in 2/4, 3/8, 4/14 or 5/20 patients. The probability of stopping under this rule is approximately 10% if the true treatment related toxicity event rate (that results in treatment discontinuation or delay in treatment administration≥ 9 weeks) is 10%, and is approximately 79% if the true treatment related toxicity event rate (that results in treatment discontinuation or delay in treatment administration≥ 9 weeks) is 30%. Enrollment will not pause, treatment

related toxicity events will be continuously monitored and the study terminated immediately if the pre- defined early-stopping rule boundary is crossed.

2. Toxicity

Adverse events will be graded according to the NCI CTCAE v4.03, presented on an individual basis and summarized using descriptive statistics.

3. Survival

Progression free survival (PFS) rate at 24 weeks, median PFS, overall survival (OS)
Overall and progression-free survival intervals will be estimated using Kaplan-Meier methodology

4. Best Objective Response by irRECIST

Best objective response rate (complete response + partial response) at 24 weeks by immune-related Response Evaluation Criteria in Solid Tumors (irRECIST), of talimogene laherparepvec in combination with pembrolizumab in patients with metastatic and/or locally advanced sarcoma.
Descriptive statistics will be provided for demographics, safety, efficacy, and biomarkers as appropriate. Patients who have not experienced the event of interest by the end of the study will be censored at the time of the last follow-up.
Due to the small sample size, the correlative studies using tumor biopsies will be exploratory and hypothesis generating in nature.
Patients evaluable for efficacy analysis will include all patients treated with talimogene laherparepvec or pembrolizumab and assessable for response. Patients who are missing an assessment of response post baseline will not be considered evaluable for response unless they missed the assessment due to progression fo disease in which case they will be considered non-responders for that time point. Patients who miss an assessment of response post baseline for any reason other than progression of disease will be replaced.
Patients evaluable for safety analysis will include all patients who have received at least one dose of talimogene laherparepvec and pembrolizumab.

We expect to accrue approximately 1-2 patients each month and hence expect to finish enrollment in 10-20 months.

Additional cohorts:

Locally advanced/metastatic cohorts:

Primary End Point

The primary objective is to evaluate the efficacy of the combination therapy in each subtype-specific cohort, as assessed by the best objective response rate (complete response + partial response). The primary endpoint is best objective response rate (RECIST 1.1). It will be estimated for each subtype-specific cohort, as the proportion of evaluable patients who have complete response and partial response as defined by RECIST 1.1 criteria, with a two

sided 95% CI provided. The lower limit of the CI allowed by a sample size of 10 is provided for a range of possible ORR in the below table.

Table 15. 95% CI for estimating ORR for a Sample Size of 10 Patients

Estimated ORR	0.20	0.30	0.40	0.50
CI 95%	0.03~0.56	0.07~0.65	0.12~0.74	0.19~0.81

Patients evaluable for efficacy analysis will include all patients who have received at least one cycle of treatment with T-VEC and pembrolizumab and are assessable for response. Patients who are missing an assessment of response post baseline will not be considered evaluable for response unless they missed the assessment due to progression of disease or treatment related toxicities in which case they will be considered non-responders for that time point. Patients who miss an assessment of response post baseline for any reason other than progression of disease and treatment related toxicity will be replaced.
In relation to the design of the additional locally advanced/metastatic cohorts, there will be 3 histology specific groups: i) cutaneous angiosarcoma, ii) epithelioid sarcoma, and iii) undifferentiated pleomorphic sarcoma/myxofibrosarcoma. These sarcoma subtypes reflect the subtypes where clinical activity was demonstrated in the phase II study to date.
We expect to accrue approximately 1-2 patients each month and hence expect to finish enrollment in 15-30 months.

Secondary endpoints
1. Safety
Patients evaluable for safety analysis will include all patients who have received at least one dose of T-VEC and pembrolizumab. Adverse events will be graded according to the NCI CTCAE v4.03, presented on an individual basis and summarized using descriptive statistics.

2. Survival
Progression free survival (PFS) rate at 24 weeks, median PFS, overall survival (OS) and progression-free survival intervals will be estimated using Kaplan-Meier methodology

3. Best Objective Response Rate by irRECIST
Best objective response rate (complete response + partial response) by 24 weeks by immune-related response criteria (irRECIST), of T-VEC in combination with pembrolizumab in patients with metastatic and/or locally advanced, sarcoma.

14.2 Correlative Endpoints Statistical Considerations

The study is not powered to detect specific hypotheses; rather this data and analysis will help better identify patients having the potential to benefit from this therapy and aid in designing larger Phase III studies.

I. To investigate the rate of seroconversion in patients HSV seronegative at baseline after initial intralesional infusion of talimogene laherparepvec. The rate of

seroconversion, after initial intralesional infusion of talimogene laherparepvec, in patients HSV seronegative at baseline will be reported using descriptive statistics.

II. To evaluate associations between selected biomarkers measured in serial peripheral blood over time with clinical efficacy, including immunophenotyping and functional analyses, evaluation of serum levels of chemokines, cytokines and other immune mediators, and characterization of T-cell receptor clonality in peripheral blood.
Summary statistics will be used to for describing changes across time. In addition the time course of biomarker measurements will be investigated graphically, by summary plots or individual patient plots; their trends over time will be categorized either by visual inspection (if there are clear trend groups such as monotonically increasing or monotonically decreasing) or by pattern recognition methods such as K-means clustering. The associations with the observed trend in selected biomarkers analyzed will be evaluated using categorical data analysis (including Fisher's exact test and logistic regression) for clinical outcome such as response and clinical benefit, and using survival data analysis (including Kaplan-Meier curve and Cox Proportional Hazards models) for survival outcomes such as progression-free survival and survival.

III. To assess the potential effect of talimogene laherparepvec cell lysis and pembrolizumab on selected biomarker expression measured in pre- and post-treatment tumor tissue and the association between these biomarkers and with clinical outcome, including characterization of PD-1/PD-L1 expression, tumor infiltrating lymphocytes (TILs) and tumor antigens, gene expression profiling, and characterization of T-cell receptor clonality in tumor-infiltrating lymphocytes (TIL). The pre- and post-treatment measurements will be compared using the paired t-test for each of these biomarkers. The associations with the selected biomarkers, in terms of both the pre-treatment measurement and the difference between pre- and post-treatment measurements, will be evaluated using the two-sample t-test for clinical outcome such as response and clinical benefit, and using survival data analysis (including Kaplan-Meier curve and Cox Proportional Hazards models) for survival outcomes such as progression-free survival and survival. More specifically, Kaplan-Meier curve and Cox Proportional Hazards models will be used for analyzing pre-treatment measurement; Kaplan-Meier curve at a landmark time point and Cox Proportional Hazards models allowing for time varying coefficients will be used for analyzing the difference between pre-and post treatment measurements.

IV. To evaluate the association between baseline tumor mutational burden and neoantigen production with clinical efficacy of the study therapy.

The associations with baseline tumor mutational burden and neoantigen production will be evaluated using categorical data analysis (including Fisher's exact test and logistic regression) for clinical outcome such as response and clinical benefit, and using survival data analysis (including Kaplan-Meier curve and Cox Proportional Hazards models) for survival outcomes such as progression-free survival and survival.

V. To evaluate pre and posttreatment magnetic resonance Images of the recurrent, resectable, sarcoma in patients in enrolled in the additional neoadjuvant cohort, to assess for definable radiological changes that can be correlated with treatment response

Summary statistics will be used to for describing changes across time. The associations between radiological changes and treatment response (clinical and pathological) will be evaluated using categorical data analysis (including Fisher's exact test and logistic regression).

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

15.2 Randomization

The study is a single-arm, non-randomized, phase II clinical trial.

16.0 DATA MANAGEMENT ISSUES

A Clinical Research Coordinator (CRC), Clinical Research Associate (CRA), and a Research Regulatory Associate (RRA) will be assigned to the study. The responsibilities of the Clinical Research Coordinator (CRC), Clinical Research Associate (CRA), and Research Regulatory Associate (RRA) include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team.

The data collected for this study will be entered into a secure database. Source documentation will be available to support the computerized patient record.

16.0.1 Data

Data: Standardized Case Report Forms (CRFs), directions for use and sign off requirements have been generated for this study. Blank case report forms will be sent to the study staff at each participating site for use. The participating Site PI is responsible for ensuring these forms are completed accurately, legibly and in a timely manner.

Source Documentation: Source documentation refers to original records of observations, clinical findings and evaluations that are subsequently recorded as data. Source documentation should be consistent with data entered into CRFs. Relevant source documentation to be submitted throughout the study includes:

- Baseline measures to assess pre–protocol disease status (ex. CT, MRI)
- Treatment records
- Grade 3-5 toxicities/adverse events not previously submitted with SAE Reports
- Response designation

16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in August 2018. The plans address the new policies set forth by the NCI in the document entitled “Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials”.

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. At a departmental/PI level, there exist procedures for quality control by the research team(s). Institutional processes in place for quality assurance include protocol monitoring, compliance and data verification audits, staff education on clinical research QA, and two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: Data and Safety Monitoring Committee (DSMC) for Phase I and II clinical trials, and the Data and Safety Monitoring Board (DSMB) for Phase III clinical trials, report to the Deputy Physician-in-Chief of Clinical Research.

The degree of monitoring required will be determined based on level of risk and documented.

The MSK DSMB monitors phase III trials and the DSMC monitors non-phase III trials. The DSMB/C have oversight over the following trials:

· MSK Investigator-Initiated Trials (IITs; MSK as sponsor)
· External studies where MSK is the data coordinating center
· Low risk studies identified as requiring DSMB/C review

The DSMC will initiate review following the enrollment of the first participant, or by the end of the year one if no accruals, and will continue for the study lifecycle until there are no participants under active therapy and the protocol has closed to accrual. The DSMB will initiate review once the protocol is open to accrual.

Final data sets for publication are required to be locked and stored centrally for potential future access requests from outside entities.

16.3 Regulatory Documentation

Prior to implementing this protocol at MSK, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MSK Institutional Review Board/Privacy Board (IRB/PB). There will be one protocol document and each participating site will utilize that document.

Participating sites that are conducting data analysis should submit this protocol to their IRB according to local guidelines. Copies of any site IRB correspondence should be forwarded to MSK.

Participating sites that are conducting data analysis must submit the following documents to MSK before specimens can be shipped to the site:

- Participating Site 1572
- Conflict of Interest forms for Participating Site Investigators on the 1572

Role of Stanford University as the participating site is as follows:

- Data analysis being performed by the site: Diagnosis, Age, Gender, ECOG, Prior therapies, All efficacy response parameters (ORR, DOR, PFS, OS) will be shared with Stanford
- The data will be shared via secure file transfer system
- The data will be shared at the end of the study
- Participant identifiers will not be shared

Role of MD Anderson Cancer Center as the participating site is as follows:

- Data analysis being performed by the site: Computational analysis of any tumor sequencing available and combining it with sequencing data available through MD Anderson cohorts. Also, genomic correlates of response to immunotherapy, histology-specific determinants of response to ICB
- Data will be shared via Secure File Transfer System
- Data will be shared as soon as possible since the study has been completed.
- Participant identifiers will not be shared. Only clinical data and demographics will be shared.

16.3.1 Amendments

Each change to the protocol document must be organized and documented by MSKCC and first approved by the MSKCC IRB/PB. Amgen has to review the protocol amendment before submission to the MSKCC IRB/PB. Upon receipt of MSKCC IRB/PB approval, MSKCC will

immediately distribute all non-expedited amendments to the participating sites, for submission to their local IRBs.

16.3.2 Additional IRB Correspondence

Continuing Review Approval
The Continuing Review Approval letter from the participating site's IRB and the most current approved version of the informed consent form should be submitted to MSKCC within 7 days of expiration. Failure to submit the re-approval in the stated timeline will result in suspension of study activities.

Deviations
A prospective protocol deviation on this study is defined as a request to treat a research participant who does not meet all the eligibility criteria, pretreatment evaluation, or who requires alteration in their study plan. If a deviation from this protocol is proposed for a potential or existing participant at MSKCC or a participating site, approval from the MSKCC IRB/PB is required prior to the action. Participating sites should contact the MSKCC PI who will in turn seek approval from the MSKCC IRB/PB.
A retrospective protocol deviation is anything that occurs with a participant, which deviated from the protocol without prior approval from the MSKCC IRB/PB. For protocol deviations that are identified after they occur, the participating site should report to MSKCC as soon as possible. The MSKCC PI will in turn report the violation to the MSKCC IRB/PB.

16.3.3 Document maintenance

The MSKCC PI and the Participating Site PI will maintain adequate and accurate records to enable the implementation of the protocol to be fully documented and the data to be subsequently verified.

The participating sites will ensure that all participating site IRB correspondence (IRB approval letters referencing protocol version date and amendment number, IRB approved protocol, appendices, informed consent forms, deviations, violations, and approval of continuing reviews) is maintained in the regulatory binder on site and sent to MSKCC.
A regulatory binder for each site will also be maintained at MSKCC; this binder may be paper or electronic. After study closure, the participating site will maintain all source documents, study related documents and CRFs for 3 years.

16.4 Noncompliance

If a participating site is noncompliant with the protocol document, accrual privileges may be suspended and/or contract payments maybe withheld (if applicable), until the outstanding issues have been resolved.

17.0 PROTECTION OF HUMAN SUBJECTS

Participation in this trial is voluntary. The patients will be explained e extent of the risks, benefits, toxicities/side effects, alternatives/options for treatment, financial costs/burdens, and the voluntary nature of the study. All patients will be required to sign a statement of informed consent, which must conform to Institutional Review Board guidelines.
Inclusion of Women and Minorities: Memorial Sloan Kettering Cancer Center has filed forms: HHS 441 (civil rights), HHS (handicapped individual), 639-A (sex discrimination), and 680 (age discrimination); we also take due notice of the NIH policy concerning inclusion of women and minorities in clinical research populations. Patients of all races, both male and female, will be accepted into the protocol. The proposed study population is as described in section 6.0.
Exclusion of Lactating or Pregnant Women: Lactating and pregnant women are also excluded because of unknown effects of talimogene laherparepvec and/or pembrolizumab that may be harmful to the developing fetus or nursing infant.
Inclusion of Children in Research: The protocol/project does not include patients younger than the age of 18. Although sarcomas are the most common solid tumor in children, pediatric sarcomas are treated with specific protocols.
Benefits: It is possible that this treatment will result in shrinkage of the tumor or in a stabilization of an otherwise progressing disease. It is not known, of course, whether these or any other favorable events will occur. It is not known whether this treatment will affect the overall survival of the patients.
Costs: The patient will be responsible for the costs of standard medical care, including all drug administration fees and all hospitalizations, even for complications of treatment. talimogene laherparepvec and/or pembrolizumab will be provided to the patient without charge. Research-only biopsies and laboratory tests will not be charged to the patient. Research testing on tissue will not be charged to the patient.
Incentives: No incentives will be offered to the patients/subjects for participation in the study.
Alternatives: For patients with locally advanced and/or metastatic sarcomas alternative treatments may include conventional cytotoxic chemotherapies including, but not limited to: doxorubicin, ifosfamide, gemcitabine in combination with docetaxel, liposomal doxorubicin, dacarbazine, temozolomide, vinorelbine; and also tyrosine kinase inhibitors depending on the histology, including, but not limited to: imatinib, sorafenib, sunitinib, pazopanib. Talimogene laherparepvec and pembrolizumab are not yet approved by the Food and Drug Administration, but may be part of the treatment in a different clinical trial.
Confidentiality: Every effort will be made to maintain the patient confidentiality. Research and hospital records are confidential. Patient’s name or any other personally identifying information will not be used in reports or publications resulting from this study. The Food and Drug Administration or other authorized agencies (e.g., qualified monitors from MSKCC or collaborating institutions) may review patients’ records and pathology slides, as required.

17.1 Privacy

MSKCC’s Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

The consent indicates that individualized de-identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers, and members

of the research teams at participating sites who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with other qualified researchers.

The consent indicates that samples and genetic information collected may be shared with other qualified researchers and placed in online databases. An example of an online database is the NIH dbGAP database, which is monitored by the National Institutes of Health, and may be made accessible to investigators approved by the U.S. government. Such information will not include identifying information such as name. It is also stated in the Research Authorization that research data (e.g. genomic sequence) may be shared with regulators.

The requirements for submission of genotype/phenotype data into the NIH dbGAP or any other public database will be followed as per the IRB SOP for Genomic Data Sharing.

17.2 Serious Adverse Event (SAE) Reporting

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

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- 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 participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted

within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following
    - An explanation of how the AE was handled
    - A description of the participant's condition
    - Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

The SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the IND Office The SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the IND Office

17.2.1 Safety Reporting to Amgen by MSKCC

The sponsor is responsible for compliance with expedited reporting requirements for serious and unexpected and related adverse events (SUSARs), for generation of SAE reports including narratives, and for periodic reporting to Amgen of SAEs as outlined in Table 17 and 18. In addition, Amgen requests additional product specific reporting as outlined in Table 18 below. Sponsor/Investigators are required to report direct exposures to talimogene laherparepvec (e.g., needle stick, splash back) of herpetic illness and all suspected herpetic events, as described in Section 2.

Table 17. Reporting Requirements for Interventional Studies

Safety Data	Timeframe for Submission to Amgen
Suspected Unexpected Serious Adverse Reaction (SUSARs)	Individual reports sent to Amgen at time of expedited reporting to IRB and/or FDA.
Serious Adverse Events (SAEs) (related)	Individual reports sent to Amgen at time of expedited reporting to IRB

	and/or FDA
Pregnancy/Lactation	Individual reports sent within 10 days of investigator awareness (Refer to Appendix D for sample of Amgen's intake forms)

Amgen Inc. FAX 888-814-8653. If FAX is unavailable: Alternative method for report submission via email svc-ags-in-us@amgen.com
Please refer to the ICH Guidelines E2A for safety related definitions and terminology: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2A/Step4/E2A_Guideline.pdf.

Table 18. Aggregate Reports

Safety Data	**Timeframe for submission to Amgen**
Adverse events (all serious and non-serious adverse events, regardless of relatedness)	Line listing and summary tabulation of **all** adverse events sent annually AND at end of study
Annual Safety Report (US IND Annual Report)	**Annually**
Other Aggregate Analyses (any report containing safety data generated during the course of a study)	**At time of ISS sponsor submission** to any body governing research conduct (e.g., RA, IRB, etc.)
Final (End of Study Report, including: • Unblinding data for blinded studies • Reports of unauthorized use of a marketed product	**At time of ISS sponsor submission** to any body governing research conduct (e.g., RA, IRB, etc.) but not later than 1 calendar year after study completion

Amgen Inc. FAX 888-814-8653. If FAX is unavailable: Alternative method for report submission via email: svc-ags-in-us@amgen.com

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.

5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form. Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

19.0 REFERENCES

1. Lindberg RD, Martin RG, Romsdahl MM, Barkley HT, Jr. Conservative surgery and postoperative radiotherapy in 300 adults with soft-tissue sarcomas. Cancer. May 15 1981;47(10):2391-2397.
2. Weitz J, Antonescu CR, Brennan MF. Localized extremity soft tissue sarcoma: improved knowledge with unchanged survival over time. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. Jul 15 2003;21(14):2719-2725.
3. Billingsley KG, Burt ME, Jara E, et al. Pulmonary metastases from soft tissue sarcoma: analysis of patterns of diseases and postmetastasis survival. Annals of surgery. May 1999;229(5):602-610; discussion 610-602.
4. Van Glabbeke M, van Oosterom AT, Oosterhuis JW, et al. Prognostic factors for the outcome of chemotherapy in advanced soft tissue sarcoma: an analysis of 2,185 patients treated with anthracycline-containing first-line regimens--a European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. Jan 1999;17(1):150-157.
5. Brennan MF AC, Maki RG. Management of Soft Tissue Sarcoma. New York: Springer 2012.
6. Coley WB. II. Contribution to the Knowledge of Sarcoma. Annals of surgery. Sep 1891;14(3):199-220.
7. Gatti RA, Good RA. Occurrence of malignancy in immunodeficiency diseases. A literature review. Cancer. Jul 1971;28(1):89-98.
8. Sorbye SW, Kilvaer T, Valkov A, et al. Prognostic impact of lymphocytes in soft tissue sarcomas. PloS one. 2011;6(1):e14611.
9. Berghuis D, Santos SJ, Baelde HJ, et al. Pro-inflammatory chemokine-chemokine receptor interactions within the Ewing sarcoma microenvironment determine CD8(+) T-lymphocyte infiltration and affect tumour progression. The Journal of pathology. Feb 2011;223(3):347-357.
10. Swann JB, Vesely MD, Silva A, et al. Demonstration of inflammation-induced cancer and cancer immunoediting during primary tumorigenesis. Proceedings of the National Academy of Sciences of the United States of America. Jan 15 2008;105(2):652-656.
11. Zhang L, Conejo-Garcia JR, Katsaros D, et al. Intratumoral T cells, recurrence, and survival in epithelial ovarian cancer. The New England journal of medicine. Jan 16 2003;348(3):203-213.
12. Balachandran VP, Cavnar MJ, Zeng S, et al. Imatinib potentiates antitumor T cell responses in gastrointestinal stromal tumor through the inhibition of Ido. Nature medicine. Sep 2011;17(9):1094-1100.
13. Brinkrolf P, Landmeier S, Altvater B, et al. A high proportion of bone marrow T cells with regulatory phenotype (CD4+CD25hiFoxP3+) in Ewing sarcoma patients is associated with metastatic disease. International journal of cancer. Journal international du cancer. Aug 15 2009;125(4):879-886.
14. Nakayama T, Tsuboyama T, Toguchida J, Hosaka T, Nakamura T. Natural course of desmoid-type fibromatosis. Journal of orthopaedic science : official journal of the Japanese Orthopaedic Association. Jan 2008;13(1):51-55.
15. Anderson PM, Meyers P, Kleinerman E, et al. Mifamurtide in metastatic and recurrent osteosarcoma: A patient access study with pharmacokinetic, pharmacodynamic, and safety assessments. Pediatric blood & cancer. Feb 2014;61(2):238-244.
16. Chou AJ, Kleinerman ES, Krailo MD, et al. Addition of muramyl tripeptide to chemotherapy for patients with newly diagnosed metastatic osteosarcoma: a report from the Children's Oncology Group. Cancer. Nov 15 2009;115(22):5339-5348.
17. Edmonson JH, Long HJ, Creagan ET, Frytak S, Sherwin SA, Chang MN. Phase II study of recombinant gamma-interferon in patients with advanced nonosseous sarcomas. Cancer treatment reports. Feb 1987;71(2):211-213.
18. Edmonson JH, Long HJ, Frytak S, Smithson WA, Itri LM. Phase II study of recombinant alfa-2a interferon in patients with advanced bone sarcomas. Cancer treatment reports. Jul-Aug 1987;71(7-8):747-748.
19. Ito H, Murakami K, Yanagawa T, et al. Effect of human leukocyte interferon on the metastatic lung tumor of osteosarcoma: case reports. Cancer. Oct 1 1980;46(7):1562-1565.
20. Rosenberg SA, Lotze MT, Yang JC, et al. Experience with the use of high-dose interleukin-2 in the treatment of 652 cancer patients. Annals of surgery. Oct 1989;210(4):474-484; discussion 484-475.
21. Schwinger W, Klass V, Benesch M, et al. Feasibility of high-dose interleukin-2 in heavily pretreated pediatric cancer patients. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. Jul 2005;16(7):1199-1206.
22. Robbins PF, Morgan RA, Feldman SA, et al. Tumor regression in patients with metastatic synovial cell sarcoma and melanoma using genetically engineered lymphocytes reactive with NY-ESO-1. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. Mar 1 2011;29(7):917-924.

23. Yu W, Fang H. Clinical trials with oncolytic adenovirus in China. Curr. Cancer Drug Targets 7, 141–148 (2007).
24. Lettieri CK, Hingorani P, Kolb EA. Progress of oncolytic viruses in sarcomas. Expert Rev. Anticancer Ther. 2012; 12(2), 229–242
25. Pol J, Bloy N, Obrist F et al. Trial watch: Oncolytic viruses for cancer therapy. Oncoimmunology 2014; 3:e28694.
26. Kim MK, Breitbach CJ, Moon A et al.Oncolytic and immunotherapeutic vaccinia induces antibody-mediated complement-dependent cancer cell lysis in humans. Sci Transl Med 2013; 5:185ra63.
27. Liikanen I, Ahtiainen L, Hirvinen ML et al. Oncolytic adenovirus with temozolomide induces autophagy and antitumor immune responses in cancer patients. Mol Ther 2013; 21:1212-23.
28. Kanerva A, Nokisalmi P, Diaconu I et al. Antiviral and antitumor T-cell immunity in patients treated with GM-CSFcoding oncolytic adenovirus. Clin Cancer Res 2013; 19:2734-44.
29. Batenchuk C, Le Boeuf F, Stubbert L et al. Non-replicating rhabdovirus-derived particles (NRRPs) eradicate acute leukemia by direct cytolysis and induction of antitumor immunity. Blood Cancer J 2013; 3:e123.
30. Toda M, Rabkin SD, Kojima H, et al. Herpes simplex virus as an in situ cancer vaccine for the induction of specific anti-tumor immunity. Hum Gene Ther 1999;10:385–93.
31. Todo T, Rabkin SD, Sundaresan P, et al. Systemic antitumor immunity in experimental brain tumor therapy using a multimutated, replication-competent herpes simplex virus. Hum Gene Ther 1999;10:2741–55.
32. Sasaki T, Tazawa H, Hasei J et al. Preclinical evaluation of telomerase-specific oncolytic virotherapy for human bone and soft tissue sarcomas. Clin. Cancer Res 2011; 17(7), 1828–1838.
33. Nemunaitis J, Tong AW, Nemunaitis M et al. A Phase I study of telomerase-specific replication competent oncolytic adenovirus (telomelysin) for various solid tumors. Mol. Ther 2010; 18(2), 429–434.
34. Rice A, Currier MA, Adams LC et al. Ewing sarcoma family of tumors express adenovirus receptors and are susceptible to adenovirus-mediated oncolysis. J. Pediatr. Hematol. Oncol. 24(7), 527–533 (2002).
35. Hoffman D, Heim A, Nettelbeck DM, Steinstraesser L, Wildner O. Evaluation of twenty human adenoviral types and one infectivity-enhanced adenovirus for the therapy of soft tissue sarcoma. Human Gene Ther 2007; 18, 51–62.
36. Opyrchal M, Aderca I, Galanis E. Phase I clinical trial of locoregional administration of the oncolytic adenovirus ONYX-015 in combination with mitomycin-C, doxorubicin, and cisplatin chemotherapy in patients with advanced sarcomas. In: Methods in Molecular Biology, Gene Therapy of Cancer (Volume 542). Walther W, Stein US (Eds). Humana Press, NY, USA, 2009: 705–717.
37. Galanis E, Okuno SH, Nascimento AG et al. Phase I–II trial of ONYX-015 in combination with MAP chemotherapy in patients with advanced sarcomas. Gene Ther. 12, 437–445 (2005).
38. Breitbach CJ, Burke JB, Jonker D. Intravenous delivery of a multi-mechanistic cancer-targeted oncolytic poxvirus in humans. Nature 477(7392), 99–102 (2011).
39. Mita AC, Sankhala K, Sarantopoulos J et al. A Phase II study of intravenous REOLYSIN (wild-type reovirus) in the treatment of patients with bone and soft tissue sarcomas metastatic to the lung. Presented at: 15th Annual Connective Tissue Oncology Society Meeting. Miami Beach, FL, USA, 5–7 November 2009.
40. Goins WF, Huang S, Cohen JB et al. Engineering HSV-1 Vectors for Gene Therapy. In: Russell J. Diefenbach and Cornel Fraefel (eds.), Herpes Simplex Virus: Methods and Protocols, Methods in Molecular Biology, vol. 1144, DOI 10.1007/978-1-4939-0428-0_5, © Springer Science+Business Media New York 2014
41. Bharatan NS, Currier MA, Cripe TP. Differential susceptibility of pediatric sarcoma cells to oncolysis by conditionally replication-competent herpes simplex viruses. J. Pediatr. Hematol. Oncol. 24(6), 447–453 (2002).
42. Currier MA, Adams LC, Mahller YY, Cripe TP. Widespread intratumoral virus distribution with fractionated injection enables local control of large human rhabdomyosarcoma xenografts by oncolytic herpes simplex viruses. Cancer Gene Ther. 12, 407–416 (2005).
43. Maldonado AR, Klanke C, Jegga AG et al. Molecular engineering and validation of an oncolytic herpes simplex virus type 1 transcriptionally targeted to midkine-positive tumors. J. Gene Med. 12, 613–623 (2010).
44. ClinicalTrials.gov. Children's Hospital Medical Center, Cincinnati. HSV1716 in Patients With Non-Central Nervous System (Non-CNS) Solid Tumors. ClinicalTrials identifier: NCT00931931 (2011). http://clinicaltrials.gov/ct2/show/ NCT00931931

45. Liu BL, Robinson M, Han ZQ, et al. ICP34.5 deleted herpes simplex virus with enhanced oncolytic, immune stimulating, andanti-tumour properties. Gene Ther. 2003;10(4):292–303.
46. Toda M, Martuza RL, Rabkin SD. Tumor growth inhibition by intratumoral inoculation of defective herpes simplex virus vectors expressing granulocyte-macrophage colony-stimulating factor. Mol Ther. 2000;2(4):324–9.
47 Hu JCC, Coffin RS, Davis CJ et al. A Phase I study of OncoVEXGM-CSF, a second-generation oncolytic herpes simplex virus expressing granulocyte macrophage colony-stimulating factor. Clin Cancer Res. 2006;12(22):6737–47.
48. Senzer NN, et al.: Phase II clinical trial of a granulocytemacrophage colony-stimulating factor-encoding, second-generation oncolytic herpesvirus in patients with unresectable metastatic melanoma. J Clin Oncol 2009;27:5763–5771
49. Andtbacka RHI, Kaufman HL, Collichio FA, et al. Talimogene Laherparepvec Improves Durable Response Rate in Patients with Advanced Melanoma. J Clin Oncol (2015):33(25):2780-278851.
50. Kaufman HL, Kim DW, DeRaffele G et al. Local and Distant Immunity Induced by Intralesional Vaccination with an Oncolytic Herpes Virus Encoding GM-CSF in Patients with Stage IIIc and IV Melanoma. Ann Surg Oncol (2010) 17:718–730.
51. Eksioglu EA, Mahmood SS, Chang M et al. GM-CSF promotes differentiation of human dendritic cells and T lymphocytes toward a predominantly type 1 proinflammatory response. Exp Hematol. 2007 Aug;35(8):1163-71
52. Shi Y, Liu CH, Roberts AI et al. Granulocyte-macrophage colony-stimulating factor (GM-CSF) and T-cell responses: what we do and don't know. Cell Research (2006)16: 126-133.
53. Benencia F, Courreges MC, FRaser NW, Coukos G. Herpes virus oncolytic therapy reverses tumor immune dysfunction and facilitates tumor antigen presentation. *Cancer Biol. Therapy* 7(8), 1194–1205 (2008).
54. Chinnery F, King CA, Elliott T et al. Viral antigen mediated NKp46 activation of NK cells results in tumor rejection via NK-DC crosstalk. Oncoimmunology 2012; 1:874-83.
55. Woller N, Kühnel F, Kubicka S. Virus infections in tumors pave the way for tumor-directed DC-vaccines. Oncoimmunology 2012; 1:208-10.
56. Donnelly OG, Errington-Mais F, Steele L et al. Measles virus causes immunogenic cell death in human melanoma. Gene Ther 2013; 20:7-15.
57. Sampath P, Li J, Hou W et al. Crosstalk between immune cell and oncolytic vaccinia therapy enhances tumor trafficking and antitumor effects. Mol Ther 2013; 21:620-8.
58. Workenhe ST, Mossman KL. Oncolytic virotherapy and immunogenic cancer cell death: sharpening the sword for improved cancer treatment strategies. Mol Ther 2014; 22:251-6.
59. Workenhe ST, Simmons G, Pol JG et al. Immunogenic HSVmediated oncolysis shapes the antitumor immune response and contributes to therapeutic efficacy. Mol Ther 2014; 22:123-31.
60. Workenhe ST, Mossman KL. Rewiring cancer cell death to enhance oncolytic viroimmunotherapy. Oncoimmunology 2013; 2:e27138.
61. Granot T, Yamanashi Y, Meruelo D. Sindbis viral vectors transiently deliver tumor-associated antigens to lymph nodes and elicit diversified antitumorCD8+ T-cell immunity. Mol Ther 2014; 22:112-22.
62. Chen DS, Mellman I. OncologyMeetsImmunology:The Cancer-ImmunityCycle. Immunity. 2013; 25;39(1):1-10
63. Peggs KS, Quezada SA, Korman AJ, Allison JP. Principles and use of anti-CTLA4 antibody in human cancer immunotherapy. Curr Opin Immunol 2006; 18: 206-213.
64. Robert C, Ghiringhelli F. What is the role of cytotoxic T lymphocyte-associated antigen 4 blockade in patients with metastatic melanoma? Oncologist 2009; 14: 848-861.
65. Hodi FS, O'Day SJ, McDermott DF et al. Improved Survival with Ipilimumab in Patients with Metastatic Melanoma. N Engl J Med 2010; NEJMoa1003466.
66. Small EJ, Tchekmedyian NS, Rini BI et al. A Pilot Trial of CTLA-4 Blockade with Human Anti-CTLA-4 in Patients with Hormone-Refractory Prostate Cancer. Clinical Cancer Research 2007; 13: 1810-1815.
67. Ansell SM, Hurvitz SA, Koenig PA et al. Phase I Study of Ipilimumab, an Anti–CTLA-4 Monoclonal Antibody, in Patients with Relapsed and Refractory B-Cell Non–Hodgkin Lymphoma. Clinical Cancer Research 2009; 15: 6446-6453.
68. Zamarin D, Holmgaard RB, Subudhi SK et al. Localized Oncolytic Virotherapy Overcomes Systemic Tumor Resistance to Immune Checkpoint Blockade Immunotherapy. Sci Transl Med 2014; 6 (226): 226-232.

69. Hodi S, Lee SJ, McDermott DF et al. Multicenter, randomized phase II trial of GM-CSF (GM) plus ipilimumab (Ipi) versus Ipi alone in metastatic melanoma: E1608. J Clin Oncol 31, 2013 (suppl; abstr CRA9007)
70. Puzanov I, Milhem MM, Andtbacka RHI et al. Primary analysis of a phase 1b multicenter trial to evaluate safety and efficacy of talimogene laherparepvec (T-VEC) and ipilimumab (ipi) in previously untreated, unresected stage IIIB-IV melanoma. J Clin Oncol 32:5s, 2014 (suppl; abstr 9029^)
71. Freeman GJ, Long AJ, Iwai Y et al. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. J Exp Med 2000; 192: 1027-1034.
72. Nishimura H, Honjo T. PD-1: an inhibitory immunoreceptor involved in peripheral tolerance. Trends Immunol 2001; 22: 265-268.
73. Carter L, Fouser LA, Jussif J et al. PD-1:PD-L inhibitory pathway affects both CD4(+) and CD8(+) T cells and is overcome by IL-2. Eur J Immunol 2002; 32: 634-643.
74. Latchman Y, Wood CR, Chernova T et al. PD-L2 is a second ligand for PD-1 and inhibits T cell activation. Nat Immunol 2001; 2: 261-268.
75. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. The New England journal of medicine. Jun 28 2012;366(26):2443-2454.
76. Movva S, Wen , Chen W et al. Predictive biomarker profiling of > 1,900 sarcomas: Identification of potential novel treatment modalities. J Clin Oncol 32:5s, 2014 (suppl; abstr 10509)
77. Patnaik A, Kang PS, Tolcher AW et al. Phase I study of MK-3475 (anti-PD-1 monoclonal antibody) in patients with advanced solid tumors. J Clin Oncol 30, 2012 (suppl; abstr 2512)
78. Hamid O, Robert C, Daud A, et al. Safety and tumor responses with lambrolizumab (Anti-PD-1) in melanoma. N Engl J Med 2013; 369:134–44.
79. Robert C, Ribas A, Wolchok JD, et al: Antiprogrammed- death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: A randomised dose-comparison cohort of a phase 1 trial. Lancet 2014; 384:1109-1117.
80. Ribas A, Hodi FS, Kefford R et al. Efficacy and safety of the anti-PD1 monoclonal antibody MK3475 in 411 patients with melanoma. J Clin Oncol 2014; 32:5s (suppl; abstr LBA9000ˆ).
81. Merelli B, Massi D, Cattaneo L, Mandala M. Targeting the PD1/PD-L1 axis in melanoma: Biological rationale, clinical challenges and opportunities. Critical reviews in oncology/hematology. Aug 28 2013.
82. van Rooij N, van Buuren MM, Philips D, et al. Tumor Exome Analysis Reveals Neoantigen-Specific T-Cell Reactivity in an Ipilimumab-Responsive Melanoma. Journal of Clinical Oncology. November 10, 2013 2013;31(32):e439-e442.
83. Lundegaard C, Lamberth K, Harndahl M, Buus S, Lund O, Nielsen M. NetMHC-3.0: accurate web accessible predictions of human, mouse and monkey MHC class I affinities for peptides of length 8-11. Nucleic acids research. Jul 1 2008;36(Web Server issue):W509-512.
84. Matsushita H, Vesely MD, Koboldt DC, et al. Cancer exome analysis reveals a T-cell-dependent mechanism of cancer immunoediting. Nature. Feb 16 2012;482(7385):400-404.
85. DuPage M, Mazumdar C, Schmidt LM, Cheung AF, Jacks T. Expression of tumour-specific antigens underlies cancer immunoediting. Nature. Feb 16 2012;482(7385):405-409.
86. Barretina J, Taylor BS, Banerji S, et al. Subtype-specific genomic alterations define new targets for soft-tissue sarcoma therapy. Nature genetics. Aug 2010;42(8):715-721.
87. Maki RG, Jungbluth AA, Gnjatic S, et al. A Pilot Study of Anti-CTLA4 Antibody Ipilimumab in Patients with Synovial Sarcoma. Sarcoma. 2013;2013:168145.
88. Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: revised RECISTguideline (version 1.1). EuropeanJournal of Cancer 2009; 45 (2): 228–247.
89. Wolchok JD, Hoos A, O'Day S, et al: Guidelines for the evaluation of immune therapy activity in solid tumors: Immune-related response criteria. Clin Cancer Res 2009; 15:7412-7420.
90. Simon R: Optimal two-stage designs for phase II clinical trials. Control Clin Trials 10:1-10, 1989
91. Long GV, D.R., Ribas A, et al. , *Safety data from the phase 1b part of the MASTERKEY-265 study combining talimogene laherparepvec (T-VEC) and pembrolizumab for unresectable stage IIIB-IV melanoma.* European Cancer Congress, 2015.
92. Hu JC, Coffin RS, Davis Cj, et al. A phase I study of OncoVEXGM-CSF, a sesond-generation oncolytic herpes simplex virus expressing granulocyte macrophage colony-stimulating factor. Clin Cancer Res (2006): 12(22): 6737-6347
93 Harrington KJ, Hingorani M, Tanay MA, et al. Phase I/II study of oncolytic HSV GM-CSF in combination with radiotherapy and cisplatin in untreated stage III/IV squamous cell cancer of the head and neck. Clin Cancer Res (2010):16(15):4005-4015

94 van der Graaf WT, Blay JY, Chawla SP, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2012:379(9829):1879-86

95 Schöffski P, Chawla S, Maki RG, et al. Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial. Lancet 2016: 387(10028):1629-37

96 Snyder A, Makarov V, Merghoub T, et al. Genetic basis for clinical response to CTLA-4 blockade in melanoma. N Engl J Med 2014: 371 (23): 2189-99

97 Lee AY, Agaram NP, Qin LX, et al. Optimal Percent Myxoid Component to Predict Outcome in High-Grade Myxofibrosarcoma and Undifferentiated Pleomorphic Sarcoma. *Ann Surg Oncol.* 2016;23(3):818-825.

98 National Comprehensive Cancer Network Guidelines for Sarcoma. 2018;2.2018: https://www.nccn.org/. Accessed 9/11/18.

99 Pervaiz N, Colterjohn N, Farrokhyar F, et al. A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma. *Cancer.* 2008;113(3):573-581.)

100 Woll PJ, Reichardt P, Le Cesne A, et al. Adjuvant chemotherapy with doxorubicin, ifosfamide, and lenograstim for resected soft-tissue sarcoma (EORTC 62931): a multicentre randomised controlled trial. *Lancet Oncol.* 2012;13(10):1045-1054.

101 Forde PM, Chaft JE, Smith KN, et al. Neoadjuvant PD-1 Blockade in Resectable Lung Cancer. N Engl J Med. 2018 May 24;378(21):1976-1986)

102 Carthon BC, Wolchok JD, Yuan J, et al. Preoperative CTLA-4 blockade: tolerability and immune monitoring in the setting of a presurgical clinical trial. Clin Cancer Res. 2010 May 15;16(10):2861-71.

103 Topalian SL, Bhatia S, Reiney Kudchadkar R, et al. Nivolumab as neoadjuvant therapy in patients with resectable Merkel cell carcinoma (MCC) in CheckMate 358. J Clin Oncol 36, 2018 (suppl; abstr 9505)

102 Burgess MA, Bolejack V, Schuetze S, et al. Clinical activity of pembrolizumab (P) in undifferentiated pleomorphic sarcoma (UPS) and dedifferentiated/pleomorphic liposarcoma (LPS): Final results of SARC028 expansion cohorts. J Clin Oncol 37, no.15 suppl (May 20, 2019) 11015-11015.

103 Chen JL, Mahoney MR, George S, et al. A multicenter phase II study of nivolumab +/- ipilimumab for patients with metastatic sarcoma (Alliance A091401): Results of expansion cohorts. *J Clin Oncol*. 2020;38(suppl 15):11511. doi:10.1200/JCO.2020.38.15_suppl.11511

104 Roland CL, Zhi-Yun Keung E, Lazar AJ, et al. Preliminary results of a phase II study of neoadjuvant checkpoint blockade for surgically resectable undifferentiated pleomorphic sarcoma (UPS) and dedifferentiated liposarcoma (DDLPS). J Clin Oncol 38, no. 15_suppl (May 20, 2020) 11505-11505.

20.0 APPENDICES:
Appendix A: Supportive care guidelines
A2.1 Pneumonitis

All attempts should be made to rule out other causes such as metastatic disease, bacterial or viral infection. It is important that patients with a suspected diagnosis of pneumonitis be managed as per the guidance below until treatment-related pneumonitis is excluded. Treatment of both a potential infectious etiology and pneumonitis in parallel may be warranted. Management of the treatment of suspected pneumonitis with steroid treatment should not be delayed for a therapeutic trial of antibiotics.

If an alternative diagnosis is established, the patient does not require management as below.

Course of Action

Grade 2 events:
- Hold pembrolizumab.
- Consider pulmonary consultation with bronchoscopy and biopsy/BAL.
- Consider ID consult
- Conduct an in person evaluation approximately twice per week
- Consider frequent Chest X-ray as part of monitoring
- Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- Second episode of pneumonitis – discontinue pembrolizumab if upon re-challenge the patient develops a second episode of Grade 2 or higher pneumonitis.

Grade 3 and 4 events:
- Discontinue pembrolizumab.
- Hospitalize patient
- Bronchoscopy with biopsy and/or BAL is recommended.
- Immediately treat with intravenous steroids (methylprednisolone 125 mg IV). When symptoms improve to Grade 1 or less, a high dose oral steroid (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours) taper should be started and continued over no less than 4 weeks.
- If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, treat with additional anti-inflammatory measures. Discontinue additional anti-inflammatory measures upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days. If symptoms worsen during steroid reduction, initiate a re-tapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer additional anti-inflammatory measures, as needed
- Add prophylactic antibiotics for opportunistic infections.

A2.2 Colitis

All attempts should be made to rule out other causes such as metastatic disease, bacterial or parasitic infection, viral gastroenteritis, or the first manifestation of an inflammatory bowel disease by examination for stool leukocytes, stool cultures, a Clostridium difficile titer and endoscopy.

Course of Action

Grade 2 Diarrhea/Colitis (4-6 stools/day over baseline, dehydration requiring IV fluids < 24 hours, abdominal pain, mucus or blood in stool):

- Hold pembrolizumab.
- Symptomatic Treatment
- For Grade 2 diarrhea that persists >1 week, and for diarrhea with blood and/or mucus,
    - Consider GI consultation and endoscopy to confirm or rule out colitis
    - Administer oral corticosteroids (prednisone 1-2 mg/kg QD or equivalent)
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- If symptoms worsen or persist > 3 days treat as Grade 3

Grade 3 Diarrhea/Colitis (or Grade 2 diarrhea that persist for greater than 3 days):

- Hold pembrolizumab.
- Rule out bowel perforation. Imaging with plain films or CT can be useful.
- Recommend consultation with Gastroenterologist and confirmation biopsy with endoscopy.
- Treat with intravenous steroids (methylprednisolone 125 mg) followed by high dose oral steroids (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours) When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Taper over 6 to 8 weeks in patients with diffuse and severe ulceration and/or bleeding.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, consider treatment with additional anti-inflammatory measures as described in the literature. Discontinue additional anti-inflammatory measures upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days. If symptoms worsen during steroid reduction, initiate a re-tapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer additional anti-inflammatory measures as needed.

Grade 4 events:

- Permanently discontinue pembrolizumab.
- Manage as per Grade 3.

A2.3 Endocrine

All attempts should be made to rule out other causes such as brain metastases, sepsis and/or infection.

Hypophysitis or other symptomatic endocrinopathy other than hypo- or hyperthyroidism

Grade 2 events:
- Hold pembrolizumab
- Monitor thyroid function or other hormonal level tests and serum chemistries more frequently until returned to baseline values.
- Pituitary gland imaging should be considered (MRIs with gadolinium and selective cuts of the pituitary can show enlargement or heterogeneity and confirm the diagnosis).
- Treat with prednisone 40 mg p.o. or equivalent per day. 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.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- Consultation with an endocrinologist may be considered.

Grade 3 events:
- Hold pembrolizumab.
- Endocrine consultation is recommended.
- Rule out infection and sepsis with appropriate cultures and imaging.
- Treat with an initial dose of methylprednisolone 1 to 2 mg/kg intravenously followed by oral prednisone 1 to 2 mg/kg per day. 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.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- Hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and electrolyte abnormalities (such as hyponatremia and hyperkalemia) constitutes adrenal crisis.
- Hospitalization and endocrine consultation should be considered.

Grade 4 events:
- Discontinue pembrolizumab.
- Manage as per Grade 3

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 events (and Grade 3-4 hypothyroidism):
- Monitor thyroid function or other hormonal level tests and serum chemistries more frequently until returned to baseline values.

- Thyroid hormone and/or steroid replacement therapy to manage adrenal insufficiency.
- Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted.
- In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
- In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care.
- Consultation with an endocrinologist may be considered.

Grade 3 hyperthyroidism events:

- Hold pembrolizumab.
- Rule out infection and sepsis with appropriate cultures and imaging.
- Treat with an initial dose of methylprednisolone 1 to 2 mg/kg intravenously followed by oral prednisone 1 to 2 mg/kg per day. 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.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:

- Discontinue pembrolizumab.
- Manage as per Grade 3

A2.4 Hematologic

All attempts should be made to rule out other causes such as metastases, sepsis and/or infection. Relevant diagnostic studies such as peripheral blood smear, reticulocyte count, LDH, haptoglobin, bone marrow biopsy or Coomb's test, etc., should be considered to confirm the diagnosis.

Course of Action
Grade 2 events:

- Hold pembrolizumab
- Prednisone 1-2 mg/kg daily may be indicated
- Consider Hematology consultation.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 3 events:

- Hematology consultation.
- Hold pembrolizumab Discontinuation should be considered as per specific protocol guidance.
- Treat with methylprednisolone 125 mg iv or prednisone 1-2 mg/kg p.o. (or equivalent) as
- appropriate

- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:
- Hematology consultation
- Discontinue pembrolizumab for all solid tumor indications; refer to protocol for hematologic
- malignancies.
- Treat with methylprednisolone

3.5 Hepatic

Course of Action

Grade 2 events:
- Hold pembrolizumab
- Monitor liver function tests more frequently until returned to baseline values (consider weekly).
- Treat with 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns
- to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic
- antibiotics for opportunistic infections, and resume pembrolizumab per protocol
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- Permanently discontinue pembrolizumab for patients with liver metastasis who begin treatment with Grade 2 elevation of AST or ALT, and AST or ALT increases ≥50% relative to baseline and lasts ≥1 week.

Grade 3 events:
- Discontinue pembrolizumab when AST or ALT >5.0 times ULN and/or total bilirubin >3.0 times ULN.
- Consider appropriate consultation and liver biopsy to establish etiology of hepatic injury, if necessary
- Treat with high-dose intravenous glucocorticosteroids for 24 to 48 hours.
    - When symptoms improve to Grade 1 or less, a steroid taper with dexamethasone 4 mg every 4 hours or prednisone at 1 to 2 mg/kg should be started and continued over no less than 4 weeks.
- If serum transaminase levels do not decrease 48 hours after initiation of systemic steroids, oral mycophenolate mofetil 500 mg every 12 hours may be given. Infliximab is not recommended due to its potential for hepatotoxicity.
- Several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:

- Permanently discontinue pembrolizumab
- Manage patient as per Grade 3 above

A2.6 Neurologic

All attempts should be made to rule out other causes such as metastatic disease, other medications or infectious causes.

Course of Action

Grade 2 events:
- Moderate (Grade 2) – consider withholding pembrolizumab.
- Consider treatment with prednisone 1-2 mg/kg p.o. daily as appropriate
- Consider Neurology consultation. Consider biopsy for confirmation of diagnosis.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 3 and 4 events:
- Discontinue pembrolizumab
- Obtain neurology consultation. Consider biopsy for confirmation of diagnosis
- Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day. If condition worsens consider IVIG or other immunosuppressive therapies as per local guidelines
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

A2.7 Ocular

All attempts should be made to rule out other causes such as metastatic disease, infection or other ocular disease (e.g. glaucoma or cataracts). However, the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:
- Evaluation by an ophthalmologist is strongly recommended.
- Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitis.
- If symptoms persist despite treatment with topical immunosuppressive therapy, consider oral steroids.
    - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 3 events:
- Evaluation by an ophthalmologist is strongly recommended

- Hold pembrolizumab and consider permanent discontinuation as per specific protocol guidance.
- Treat with systemic corticosteroids such as prednisone at a dose of 1 to 2 mg/kg per day.
    - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:
- Evaluation by an ophthalmologist is strongly recommended
- Permanently discontinue pembrolizumab.
- Treat with corticosteroids as per Grade 3 above

A2.8 Renal

All attempts should be made to rule out other causes such as obstructive uropathy, progression of disease, or injury due to other chemotherapy agents. A renal consultation is recommended. However, the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:
- Hold pembrolizumab
- Treatment with prednisone 1-2 mg/kg p.o. daily.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 3-4 events:
- Discontinue pembrolizumab
- Renal consultation with consideration of ultrasound and/or biopsy as appropriate
- Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone IV or equivalent once per day.
    - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

A2.9 Skin - Rash and Pruritus

Course of Action

Grade 2 events:
- Symptomatic treatment should be given such as topical glucocorticosteroids (e.g., betamethasone 0.1% cream or hydrocortisone 1%) or urea-containing creams in combination with oral antipruritics (e.g., diphenhydramine HCl or hydroxyzine HCl).
- Treatment with oral steroids is at physician’s discretion for Grade 2 events.

Grade 3 events:
- Hold pembrolizumab.

- Consider Dermatology Consultation and biopsy for confirmation of diagnosis.
- Treatment with oral steroids is recommended, starting with 1 mg/kg prednisone or equivalent once per day or dexamethasone 4 mg four times orally daily.
    - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:

- Permanently discontinue pembrolizumab.
- Dermatology consultation and consideration of biopsy and clinical dermatology photograph.
- Initiate steroids at 1 to 2 mg/kg prednisone or equivalent.
    - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

A2.10 Other

All attempts should be made to rule out other causes. Therapeutic specialists should be consulted as appropriate.

Course of Action

Grade 2 events or Grade 1 events that do not improve with symptomatic treatment:

- Withhold pembrolizumab.
- Systemic corticosteroids may be indicated.
- Consider biopsy for confirmation of diagnosis.
- If pembrolizumab held and corticosteroid required, manage as per grade 3 below.

Grade 3 events:

- Hold pembrolizumab
- Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks. Otherwise, pembrolizumab treatment may be restarted and the dose modified as specified in the protocol

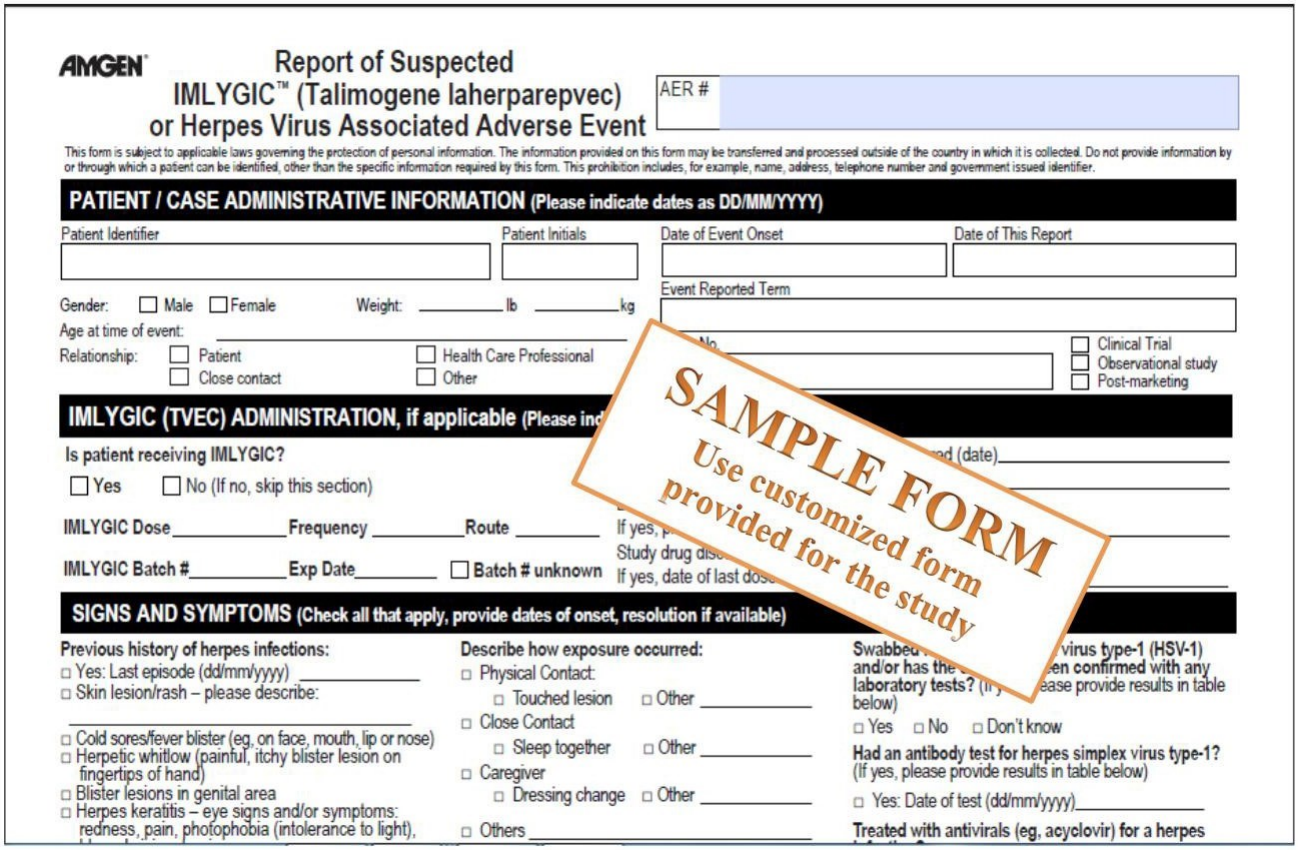
Grade 4 events:

- Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day.
- Discontinue pembrolizumab

Appendix B. Guidelines for the management of pembrolizumab infusion and hypersensitivity reactions.

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDS • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop recurrent Grade 2 infusion reaction despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: • Diphenhydramine 50mg p.o. (or equivalent dose of antihistamine). • Acetaminophen 500-1000mg p.o. (or equivalent dose of antipyretic).
Grades 3 or 4 **Grade 3:** Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) **Grade 4:** Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDS • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids • Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing

APPENDIX C: Sample of Report of Suspected IMLYGICTM (Talimogene laherparepvec) or Herpes Virus Associated Adverse Event



AMGEN

Report of Suspected
IMLYGIC™ (Talimogene laherparepvec)
or Herpes Virus Associated Adverse Event

AER #

This form is subject to applicable laws governing the protection of personal information. The information provided on this form may be transferred and processed outside of the country in which it is collected. Do not provide information by or through which a patient can be identified, other than the specific information required by this form. This prohibition includes, for example, name, address, telephone number and government issued identifier.

PATIENT / CASE ADMINISTRATIVE INFORMATION (Please indicate dates as DD/MM/YYYY)

Patient Identifier | Patient Initials | Date of Event Onset | Date of This Report

Gender: ☐ Male ☐ Female Weight: _____ lb _____ kg

Age at time of event: _____

Relationship: ☐ Patient ☐ Health Care Professional ☐ Close contact ☐ Other

Event Reported Term

No.

☐ Clinical Trial ☐ Observational study ☐ Post-marketing

IMLYGIC (TVEC) ADMINISTRATION, if applicable (Please ind

Is patient receiving IMLYGIC?

☐ Yes ☐ No (If no, skip this section)

IMLYGIC Dose _____ Frequency _____ Route _____

IMLYGIC Batch # _____ Exp Date _____ ☐ Batch # unknown

SIGNS AND SYMPTOMS (Check all that apply, provide dates of onset, resolution if available)

Previous history of herpes infections:
- ☐ Yes: Last episode (dd/mm/yyyy) _____
- ☐ Skin lesion/rash – please describe: _____
- ☐ Cold sores/fever blister (eg, on face, mouth, lip or nose)
- ☐ Herpetic whitlow (painful, itchy blister lesion on fingertips of hand)
- ☐ Blister lesions in genital area
- ☐ Herpes keratitis – eye signs and/or symptoms: redness, pain, photophobia (intolerance to light),

Describe how exposure occurred:
- ☐ Physical Contact:
  - ☐ Touched lesion ☐ Other _____
- ☐ Close Contact
  - ☐ Sleep together ☐ Other _____
- ☐ Caregiver
  - ☐ Dressing change ☐ Other _____
- ☐ Others _____

Swabbed … virus type-1 (HSV-1) and/or has the … been confirmed with any laboratory tests? (If … please provide results in table below)

☐ Yes ☐ No ☐ Don't know

Had an antibody test for herpes simplex virus type-1? (If yes, please provide results in table below)

☐ Yes: Date of test (dd/mm/yyyy) _____

Treated with antivirals (eg, acyclovir) for a herpes

SAMPLE FORM
Use customized form provided for the study

APPENDIX D: Reporting to Amgen of Pregnancy or Lactation – Notification Worksheets

Sample of Pregnancy Notification

AMGEN® Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: _____

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (_____)_____ **Fax** (_____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject DOB:** mm_____ / dd_____/ yyyy_____

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm_____/dd_____/yyyy_____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's LMP mm_____ / dd_____/ yyyy_____ ☐ Unknown

Estimated date of delivery mm_____ / dd_____/ yyyy_____ ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm_____ / dd_____/ yyyy_____

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery: mm _____/ dd_____/ yyyy_____

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Amgen maintains a Pregnancy Surveillance Program that collects data about pregnancy of women who have been exposed to an Amgen product directly or via male sexual partner. Information from this program and from other sources of information, will contribute to knowledge that ultimately could help patients and their doctors in the future make more informed decisions about taking an Amgen medication during pregnancy.

Effective Date: March 27, 2011

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Sample of Lactation Notification Worksheet

Print Form

AMGEN® Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line
SELECT OR TYPE IN A FAX# enter fax number

1. Case Administrative Information

Protocol/Study Number: _____

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (_____)_____ **Fax** (_____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Date of Birth:** mm_____ / dd_____/ yyyy_____

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm_____/dd_____/yyyy_____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Amgen maintains a Lactation Surveillance Program that collects data about women who have been exposed to an Amgen product while breastfeeding. Information from this program and from other sources of information will contribute to knowledge that ultimately could help patients and their doctors in the future make more informed decisions about taking an Amgen medication during lactation.

Effective Date: 03 April 2012, version 2.

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Appendix E: Sample of Serious Adverse Event form

Serious Adverse Drug Reaction
Investigator Sponsored Study
Amgen ISS
FAX Transmittal Form
talimogene laherparepvec (T-Vec)

Amgen study number 20149187 / IRB#16-1534

To: Amgen Global Safety Toll-free #:1-888-814-8653 *For countries where the U.S. toll-free # cannot be used*: +44-20-7136-1046 Email (*Only* for sponsors with a secure email connection with Amgen): svc-ags-in-us@amgen.com	**AMGEN ISS PROTOCOL #:** 20149187 Sponsor: Memorial Sloan Kettering Cancer Center Sponsor Contact Name: _____ Fax No:_____ Phone No:_____ Date: _____

Use this form as a cover page for an individual report, for batched individual reports, and for line listings.
******NOTE: Please use data reconciliation fax cover sheet to submit data reconciliation line listings.***

Fax transmission contents (Check all that apply):

To be sent immediately after each single case submission to RA, EC, IRB or DMC:

☐ Expeditable Serious Adverse Events/Serious Adverse Drug Reactions # of Reports Submitted: _____

To be sent in regular intervals per contractual agreement (eg, as batched individual reports or line listings):

☐ Serious Adverse Drug Reactions # of Reports Submitted: _____
Period from _____ to _____
DD/MMM/YYYY DD/MMM/YYYY

☐ Serious Adverse Events # of Reports Submitted: _____
(does NOT apply for marketed Amgen products)
Period from _____ to _____
DD/MMM/YYYY DD/MMM/YYYY

Other Reports (to be sent as per contractual agreement eg, pregnancy/lactation reports)

☐ Specify type of report: _____ # of Reports Submitted: _____
Period from _____ to _____
DD/MMM/YYYY DD/MMM/YYYY

For multi-country studies please indicate countries of transmitted report(s) origin:

Total # of pages in this transmission, including cover page: _____

Version date 01May2013

Appendix F: Procedure for Research Blood and Biopsy Collection

Research Biopsy Collection

Given the requirement for fresh and frozen tissue, FFPE archival samples cannot be substituted for the baseline or subsequent biopsies.

The same metastatic tumor site should be biopsied at each time point if feasible. Cores will be representative of tumor and obtained with 18-gauge needles where appropriate and be of at least 1cm in length. Cores will be representative of tumor, and targeted to the de-differentiated component in the case of de-differentiated liposarcoma.
The quality, viability and tumor content of biopsies will be confirmed by the on-call clinical pathologist at the time of retrieval.
A goal of 6 cores should be obtained with a minimum of one formalin-fixed, one fresh and one flash frozen in liquid nitrogen.

1 FFPE
2 Fresh
3 Flash frozen
4 Fresh
5 Flash frozen
6 Flash frozen

FFPE cores should be placed in formaldehyde solution and sent to the central pathology lab.
Fresh core should be placed in RPMI media in a falcon tube and transported on ice (RPMI media should be kept in a fridge and should not be kept longer than two weeks)
Flash frozen cores should be placed in a clean cryovial (nunc tube) then placed in liquid nitrogen for at least 2 minutes, transported in preferably a dewar flask of liquid nitrogen or in dry ice.
If any extra cores are obtained, they should be flash frozen with liquid nitrogen as above.
Samples will be labeled using an adherent, liquid nitrogen proof label with the following information

1) Procurement date
2) Study IRB number
3) Study patient number
4) Time point (baseline or on-treatment)
5) Anatomical biopsy site

Research blood collection

At each research blood collection time point the following samples will be collected:
4x8ml of peripheral venous blood will be collected in green/red speckled top CPT vacutainer tubes. The tubes will be inverted 8-10 times to mix the sodium heparin solution. Specimens will be placed in a biohazard bag and kept at room temperature.
Samples will be labeled with the following information:

1) Procurement date
2) Study IRB number
3) Study patient number
4) Time point (baseline or week-X)

Laboratory Contact Details
Research blood samples and tumor biopsy samples, along with completed requisition forms, are to be transported to the Immune Monitoring Facility in the Zuckerman Research Bldg, Room Z-1513. At least 24 hr advanced notification prior to biopsy or blood collection must be provided by email to the IMF contacts below or entered in the IMF shared calendar

(zzCAL_LAB_Clinical_Trials/Shared Calendar), with clinical site location and contact information from which samples are arriving indicated. Samples must be delivered between the hours of 9 am-4 pm to a member of the lab.
Rosemarie Ramsawak <ramsawar@mskcc.org> 646-888-3106
Zhenyu Mu <muz@mskcc.org> 646-888-2114
Kevin Crawford <crawfork@mskcc.org> 646-888-3106
Luisa Caro <carol@mskcc.org> 646-888-3106