A Phase II Randomized Trial of Intralesional Talimogene Laherparepvec (TALIMOGENE LAHERPAREPVEC) with or without Hypofractionated Radiotherapy for Cutaneous Melanoma, Merkel Cell Carcinoma, or Other Solid Tumors

PROTOCOL FACE PAGE FOR
MSK THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

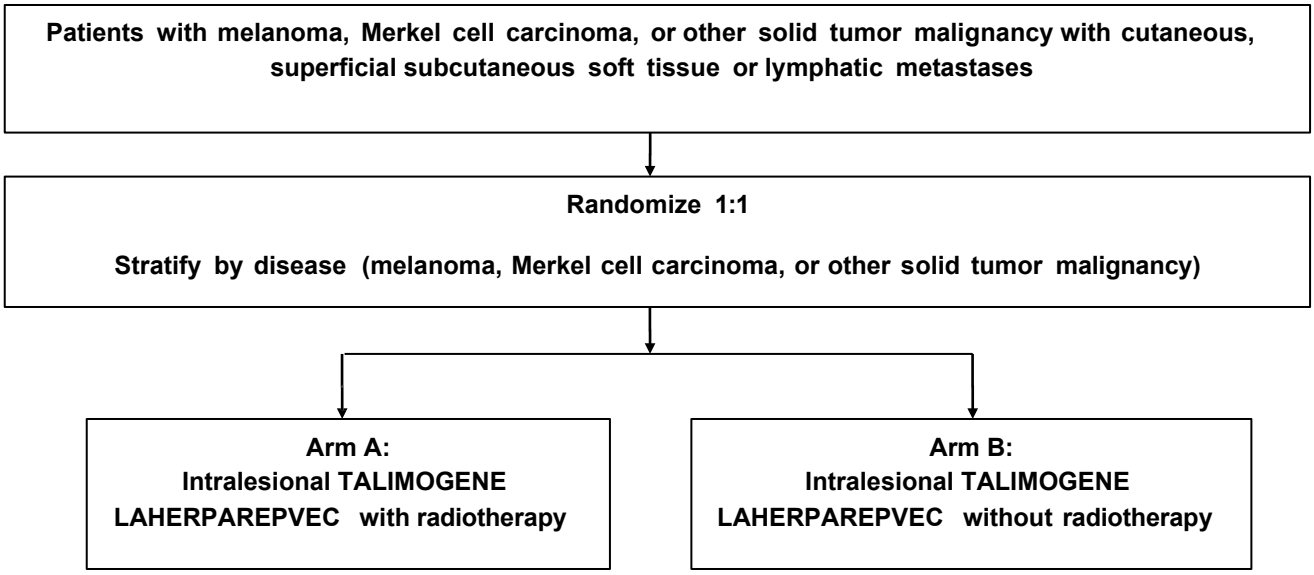
This is a randomized phase II study entitled "A Phase II Randomized Trial of Intralesional Talimogene Laherparepvec with or without Hypofractionated Radiotherapy for Cutaneous Melanoma or Merkel Cell Carcinoma, or Other Solid Tumors." Patients with cutaneous metastases from melanoma, Merkel cell carcinoma, and other solid tumor malignancies will be studied. Patients must have at least one cutaneous metastasis amenable to intralesional oncolytic immunotherapy with Talimogene Laherparepvec and radiotherapy and one metastasis amenable to observation.

The primary objective of the study is to characterize the systemic response of metastases not injected or irradiated in patients treated with Talimogene Laherparepvec with or without radiotherapy.

The secondary objectives of the study are to characterize the clinical efficacy, safety, patient reported quality of life, duration of response, time to response onset, progression free and overall survival associated with the treatment of patients with Talimogene Laherparepvec with or without radiotherapy.

The exploratory objective of the study is to characterize the immunologic response associated with the treatment of patients with Talimogene Laherparepvec with or without radiotherapy.

It is estimated that a minimum of 18 and a maximum of 34 patients will be enrolled over a minimum of 2 and a maximum of 3 years to complete the study over a minimum of 3 and a maximum of 4-year time period.



2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objectives:

1. To assess the systemic efficacy of Talimogene Laherparepvec with or without radiotherapy in patients with cutaneous metastases from melanoma, Merkel cell

carcinoma, or other solid tumor malignancy. Systemic efficacy will be measured by the subject level modified WHO (mWHO) defined response of a metastasis not injected with Talimogene Laherparepvec or irradiated 16 weeks after initiation of therapy. A systemic response rate of ≤ 7.5% is unacceptable and a rate of ≥ 27% is acceptable (for both arms).

Secondary Objectives:

1. To assess the clinical efficacy of Talimogene Laherparepvec with or without radiotherapy in patients with cutaneous metastases from melanoma, Merkel cell carcinoma, or other solid tumor malignancy. Clinical efficacy will be measured by determining the objective response rate (ORR) defined as patients achieving complete response or partial response defined by the modified World Health Organization (mWHO) criteria. Response will be assessed approximately 16 weeks after the first treatment. Among patients randomized to receive Talimogene Laherparepvec, we expect ORRs to be comparable to previous studies (26.4% 95% CI 21.4-31.5%). Patients randomized to receive Talimogene Laherparepvec and radiotherapy are expected to have ORRs higher than previously published studies of Talimogene Laherparepvec alone.

2. To assess the safety of Talimogene Laherparepvec with or without radiotherapy in patients with cutaneous metastases from melanoma, Merkel cell carcinoma, or other solid tumor malignancy as measured by the frequency of adverse events (grade 2-5 adverse events). The window for adverse event assessment will include the 20 week time period from first treatment until 5 weeks after last treatment. We expect that frequency and grade of adverse events in patients receiving Talimogene Laherparepvec will be similar to previous studies of Talimogene Laherparepvec alone, and that radiotherapy will increase the frequency and grade of adverse events.

3. To evaluate the patient reported quality of life following Talimogene Laherparepvec with or without radiotherapy in patients with cutaneous metastases from melanoma, Merkel cell carcinoma, or other solid tumor malignancies treated with Talimogene Laherparepvec with or without hypofractionated radiotherapy. It is expected that quality of life (described further in section 12.0) will improve after Talimogene Laherparepvec with or without radiotherapy.

4. To assess the duration of response (DOR) in patients achieving a partial or complete response. DOR will be defined as the duration of time from occurrence of partial or complete response until first occurrence of progression or date of death if the patient dies due to any causes before progression.

5. To assess the time to response onset in following Talimogene Laherparepvec with or without radiotherapy. It is expected that the time to response onset in patients randomized to receive Talimogene Laherparepvec will be similar to previous studies of Talimogene Laherparepvec alone (median 4.1 months, range 1.2-16.9 months). It is anticipated that the time to response onset in patients receiving Talimogene Laherparepvec and radiotherapy will be earlier than prior studies of Talimogene Laherparepvec alone.

6. To estimate progression free and overall survival in patients receiving Talimogene Laherparepvec with or without radiotherapy for cutaneous metastases from melanoma and Merkel cell carcinoma. Progression free survival will be defined as the time elapsed from start of protocol treatment until progression (according to mWHO criteria) or death.

Exploratory Objectives:

1. To characterize the immunologic response to Talimogene Laherparepvec with or without radiotherapy in patients with cutaneous metastases from melanoma, Merkel cell carcinoma, or other solid malignancies. Tumor biopsies and peripheral blood specimens will be used to characterize immunologic effects of treatment such as tumor infiltrating lymphocytes and peripheral blood immunophenotype, serum antibody titers and cytokine array analyses.

3.0 BACKGROUND AND RATIONALE

Cutaneous metastases. Secondary malignant neoplasms of the skin (also referred to as cutaneous metastases) are not infrequently encountered in patients with advanced cancer. According to one study, 5.3% of patients with solid tumors develop cutaneous metastases (Krathen RA South Med J 2003). Practically, the anatomic compartment of "cutaneous metastases" includes the skin (cutis) and superficial subcutaneous soft tissues and lymphatics (in-transit channels as well as lymph nodes). The disorder is especially common in high-risk skin malignancies, including melanoma and Merkel cell carcinoma. Cutaneous metastases can lead to problems such as infection, hemorrhage, and discomfort. One study demonstrated that the presence of cutaneous metastases was the single most deleterious factor in patient quality of life (Shimozuma K Surg Today 1995). Surgical excision may be a simple and effective means of dealing with cutaneous metastasis, but is not always possible because of patient comorbidities or extent of the cutaneous metastases. Systemic therapy alone often has limited efficacy for cutaneous metastases (Richtig E Br J Dermatol 2005). We have recently reported on the efficacy of a variety of skin-directed therapies (such as radiation therapy and intralesional therapy) for cutaneous metastases, and found that treatment is well-tolerated, associated with improvements in quality of life, and frequently leads to reduction in size of the treated tumor (Spratt DE J Clin Oncol 2014). The systemic efficacy of skin-directed therapy on non-treated metastases has not been well-characterized.

Radiotherapy for cutaneous metastases. Radiotherapy has been used for many years as a palliative treatment for cutaneous metastases. Our recent meta-analysis of skin-directed therapies for cutaneous metastases demonstrated that radiotherapy yields a complete response in 62.7% (95% CI 22.8-90.5%), and an objective response in 83.8% (95% CI 37.9-97.8%). Moreover, studies that combined radiotherapy with other skin-directed therapies (intralesional therapy or topical therapy) demonstrated even higher overall response rates (Spratt DE J Clin Oncol 2014). As noted above, the systemic efficacy to skin-directed radiotherapy has not been well-characterized. However, studies from our group and others have suggested that radiotherapy may augment immunologic response to produce systemic responses in non-irradiated metastases (Postow M N Engl J Med 2011, Barker CA Cancer Immunol Res 2013, Teulings H Br J Derm 2013).

Talimogene laherparepvec (TALIMOGENE LAHERPAREPVEC) for cutaneous metastases. Talimogene laherparepvec (TALIMOGENE LAHERPAREPVEC) is an intralesional oncolytic immunotherapy consisting of a modified type-1 herpes simplex virus that selectively replicates in malignant cells and stimulates an immune response. A phase I trial of Talimogene Laherparepvec (formerly OncoVEX^{GM-CSF}) in 30 patients with cutaneous or subcutaneous metastases from a variety of malignancies (breast, head and neck, melanoma, gastrointestinal) who had failed prior therapy demonstrated the safety of this approach (Hu JC Clin Cancer Res 2006). A subsequent phase II study of 50 patients with cutaneous metastases from melanoma demonstrated an overall response rate of 26%, an revealed responses of metastases that were not injected (Senzer NN J Clin Oncol 2009). Correlative analyses suggested that response in metastases that were not injected were due to immunologic effects of Talimogene Laherparepvec (Kaufman HL Ann Surg Oncol 2010). Preliminary results of a phase III study of Talimogene Laherparepvec versus granulocyte monocyte colony stimulating factor (GM-CSF) for patients with unresectable stage IIIB-IV melanoma have been presented, and demonstrated an overall response rate of 26.4% (95% CI 2.7-29.2%), with a trend toward improved overall survival (Andtbacka RHI ASCO 2013). Responses were seen most often at the site of the injected cutaneous metastasis (64.3%), but also in non-injected cutaneous metastases (33.7%), and non-injected visceral metastases (15.2%). Importantly, the median time to response was 16 weeks, therefore approximately 7.5% of patients are expected to have response in uninjected metastases at this time point (Andtbacka RHI HemOnc Today Melanoma and Cutaneous Malignancies Meeting 2014). Increasing the response rate by combining Talimogene Laherparepvec with other therapies is an active area of study.

Preclinical rationale for combining TALIMOGENE LAHERPAREPVEC with radiotherapy. As previously reviewed, there is an abundance of preclinical literature to suggest that combining oncolytic immunotherapy (such as TALIMOGENE LAHERPAREPVEC) with radiotherapy can increase the antineoplastic effects of each treatment modality (Touchefeu Y Rad Onc 2011, Advani S IJROBP 2006). Irradiation of cancer cells can increase viral uptake, replication, gene expression and the induction of host cell death, thereby enhancing the effects of oncolytic immunotherapy (see Figure 1). Conversely, viral proteins can inhibit components of the DNA damage response pathway, thereby sensitizing cancer cells to the effects of radiation therapy (see Figure 2).

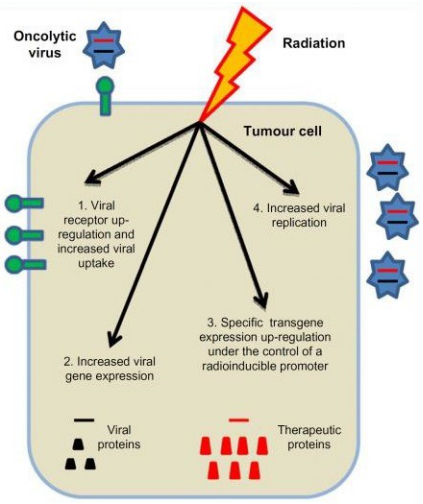


Figure 1. Mechanisms through which ionizing radiation may enhance oncolytic immunotherapy. From Touchefeu Y Radiother Oncol 2011.

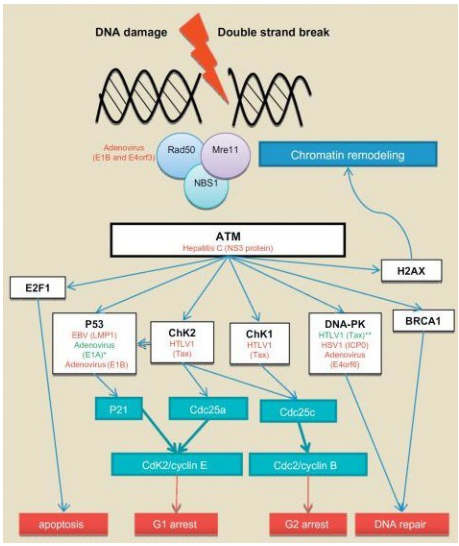


Figure 2. Mechanisms through which oncolytic immunotherapy may enhance radiotherapy. From Touchefeu Y Radiother Oncol 2011.

Clinical experience combining TALIMOGENE LAHERPAREPVEC and radiotherapy. Several studies have investigated the combination of oncolytic immunotherapy (such as TALIMOGENE LAHERPAREPVEC) and radiotherapy. Most relevant to the current protocol is a phase I/II trial of Talimogene Laherparepvec (formerly OncoVEX^{GM-CSF}) and chemoradiation therapy that was reported in 2010 (Harrington KJ Clin Cancer Res 2010). Seventeen patients with locally advanced mucosal squamous cell carcinoma of the head and neck (mSCCHN) underwent high dose radiotherapy (70 Gy in 35 fractions), with concomitant cisplatin chemotherapy (100 mg/m^2) and escalating doses (10^6 – 10^8 plaque forming units (pfu)/mL) of intralesional Talimogene Laherparepvec during radiotherapy (day 1, 22, 43 and 64, see Figure 3). Escalating doses of Talimogene Laherparepvec were delivered without observation of dose limiting toxicities. Adverse events (AEs) were consistent with those normally observed during standard chemoradiation therapy for locally advanced mSCCHN), and grade 3 or 4 observed in ≥2 patients were unrelated to Talimogene Laherparepvec dose. The recommended dose of Talimogene Laherparepvec for concomitant administration with radiotherapy in future studies of mSCCHN was 10^6 followed by 10^8. This dosing schedule is consistent with previous and ongoing studies in melanoma, and other diseases (Figure 3).

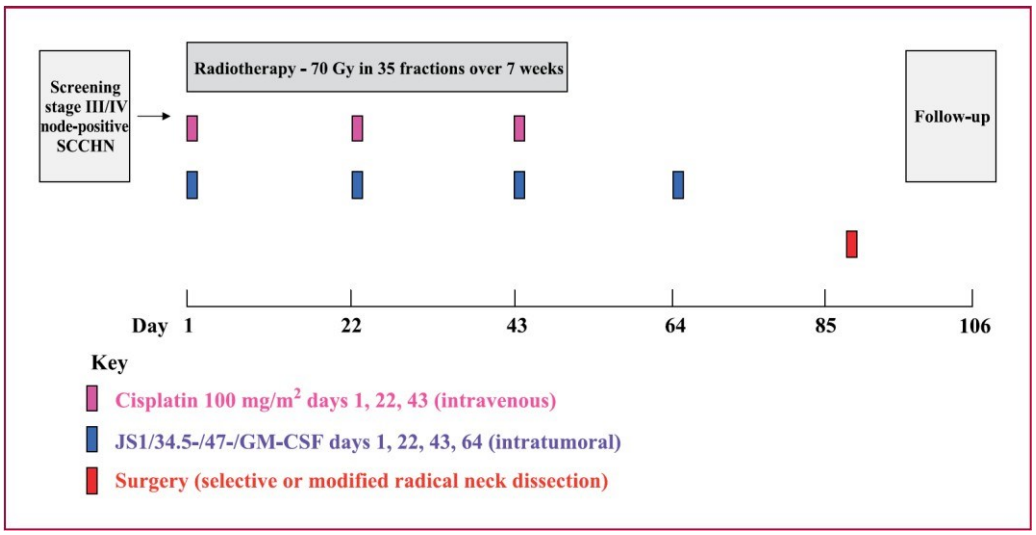


Figure 3. Schedule of concurrent T-VEC and chemoradiotherapy in a previously reported phase I/II clinical trial. From Harrington KJ Clin Cancer Res 2010.

The efficacy of this combination was promising. At a median follow-up of 29 months, 100% of patients achieved locoregional disease control, and 76.5% of patients were relapse-free. Notably, no patient participating in this study had measurable metastases that were not irradiated or injected with Talimogene Laherparepvec (Harrington KJ Clin Cancer Res 2010). Therefore, the systemic efficacy of this therapeutic combination was not assessed.

Combining immunotherapy and radiotherapy. We have previously reviewed and reported on the combinations of radiotherapy and immunotherapy (Barker and Postow IJROBP 2014). Of particular interest is the ability of the radiotherapy to augment the systemic response to immunotherapy. Evidence of this phenomenon is demonstrated by the abscopal effect, or regression of a non-irradiated tumor after radiotherapy. Investigators have previously found that the combination of granulocyte-monocyte colony stimulating factor (GM-CSF) and radiotherapy can produce an abscopal effect in 27% of patients. In the OPTiM trial described above, patients treated with GM-CSF demonstrated a non-injected visceral response rate of <5%, while those treated with Talimogene Laherparepvec demonstrated a non-injected visceral metastasis response rate of 15.2%. Whether radiotherapy combined with Talimogene Laherparepvec can increase the response rate among non-injected visceral metastases is unknown. Given that systemic response of visceral metastases that have not been injected or irradiated is a sign of successful immunotherapy, it is this endpoint that is of considerable interest for investigation.

To our knowledge, a study of Talimogene Laherparepvec and radiotherapy to characterize the systemic efficacy of this therapeutic combination has never been performed, and has not been initiated elsewhere. The present study will provide information for society regarding the potential benefit of this therapeutic combination. For patients with cutaneous metastases from melanoma, Merkel cell carcinoma, or other solid tumor malignancy this study may provide valuable therapeutic benefit from treatment using 2 active agents.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is a prospective, single site phase II randomized trial examining the systemic efficacy (primary objective), clinical efficacy, safety, quality of life effects, duration of response, time to response, progression-free and overall survival (secondary objectives) of patients of Talimogene Laherparepvec with or without radiotherapy in patients with cutaneous metastases from melanoma, Merkel cell carcinoma, or other solid tumor malignancies.

4.2 Intervention

Patients with cutaneous metastases from melanoma, Merkel cell carcinoma or other solid tumor malignancy will be screened for eligibility. If a patient is found to have anything other than cutaneous metastases from melanoma, Merkel cell carcinoma or other solid tumor malignancy, appropriate clinical management will be undertaken.

If eligible, patients will undergo baseline PET/CT imaging, quality of life assessment, followed by intralesional Talimogene Laherparepvec with or without radiotherapy.

Talimogene Laherparepvec will be administered at weeks 0, 3, 5, 7, 9, 11, 13 and 15. The first dose of Talimogene Laherparepvec will be 10^6 plaque forming units (PFU)/mL, followed three weeks later by a dose of 10^8 pfu/mL. Up to 4 mL will be injected at each treatment. Metastases will be injected, beginning with the largest tumor first, with volumes indicated below, until a maximum of 4 mL has been used.

Tumor size (longest dimension)	Talimogene laherparepvec (TVEC) injection volume	Dose concentration
>5 cm	≤4 mL	10^6 PFU/mL at week 0, 10^8 PFU/mL thereafter
2.6-5 cm	≤2 mL	10^6 PFU/mL at week 0, 10^8 PFU/mL thereafter
1.6-2.5 cm	≤1 mL	10^6 PFU/mL at week 0, 10^8 PFU/mL thereafter
0.6-1.5 cm	≤0.5 mL	10^6 PFU/mL at week 0, 10^8 PFU/mL thereafter
≤0.5 cm	≤0.1 mL	10^6 PFU/mL at week 0, 10^8 PFU/mL thereafter

Table 1. TALIMOGENE LAHERPAREPVEC injection volume and concentration based on tumor size.

Patients randomized to Arm A will receive 3 radiotherapy treatments (one treatment every 3-6 days) during weeks 3 and 4. The first treatment will occur 6 (+/- 2) hours after the Talimogene Laherparepvec administration at week 3.

Patients randomized to Arm B will receive Talimogene Laherparepvec alone, as described above, without radiotherapy.

Patients will undergo disease re-evaluation with PET/CT and quality of life assessment at week 16.

Patients with potential for clinical benefit may continue Talimogene Laherparepvec every 2 weeks, after week 15, for up to 24 weeks. This will be determined by the treating clinician.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

Please see Investigational Product Information – Talimogene Laherparepvec (AMG 678). The agent is under review by the FDA for use in patients with melanoma and will be used under a cross-referenced IND for use in other diseases.

External beam radiation therapy is a standard, non-investigational treatment for cutaneous metastasis.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

- Man or woman ≥ 18 years old
- Life expectancy > 4 months
- Histopathologically confirmed melanoma, Merkel cell carcinoma or other solid tumor malignancy
- Cutaneous, subcutaneous soft tissue, or superficial lymphatic metastasis not suitable for surgical resection
- Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2
- Cutaneous, subcutaneous soft tissue, or superficial lymphatic metastasis that is amenable to injection and irradiation and > 10 mm in longest dimension
    - Cutaneous metastasis in a region of previous radiation therapy is amenable to radiation therapy as part of this protocol if at least 6 months has elapsed since prior radiotherapy and the dose of radiotherapy previously administered did not exceed an equivalent dose of 60 Gy in 2 Gy equivalent fractions at the skin surface (using linear-quadratic modeling with alpha/beta=11.5)
- Metastasis that is > 10 mm in longest dimension or exhibits radiotracer uptake consistent with metastasis on PET/CT
- Adequate coagulation function (platelet count >50 k/mcL, international normalized ratio of < 1.5)
- Resolution or stabilization of clinically significant adverse events from prior therapy
- Able to provide valid written informed consent

6.2 Subject Exclusion Criteria

- Active herpetic skin lesions or prior complications of HSV-1 infection (such as herpetic keratitis, herpetic encephalitis)
- Receipt of a therapeutic anticoagulant
- Receipt of live vaccine within 28 days of planned first dose of TVEC

- Receipt of another cancer therapy (targeted therapy, chemotherapy, investigational therapy, immunotherapy, radiotherapy or surgery) which is yielding an overall response (by response criteria in this study)
    - Patients with stable or progressing disease (as determined by at least 2 consecutive assessments at 6-week interval) can continue to receive the same therapy during treatment as part of this protocol
- History of symptomatic autoimmune disease (such as lupus, scleroderma, Crohn's disease, ulcerative colitis) requiring systemic treatment (for example corticosteroids or immunosuppressants); replacement therapy (for example, thyroxine, insulin) is not considered a systemic treatment
- History of high grade (CTCAE $\geq$ Grade 3) immune mediated adverse event from prior cancer immunotherapy
- History of CTCAE $\geq$ Grade 2 immune mediated endocrinopathy from prior cancer immunotherapy
- Intermittent or chronic use of oral or intravenous antiherpetic drug (such as acyclovir)
- Active or chronic hepatitis B or C infection
    - Previously infected with evidence of immunity and no evidence of active hepatitis is not an exclusion criterion
- Known human immunodeficiency virus (HIV) infection
- Known leukemia or lymphoma
- Common variable immunodeficiency
- Patients requiring chronic high dose immunosuppressants including steroids (prednisone daily equivalent of ≥ 10 mg)
- Known severe congenital or acquired cellular or humoral immunodeficient or immunocompromised patients (as noted in Investigators Brochure and Developmental Core Safety Information)
- High likelihood of protocol non-compliance (in opinion of investigator)
- Woman of childbearing potential unwilling to use effective contraception during protocol treatment and for 3 months after last dose of Talimogene Laherparepvec
- Woman of childbearing potential that is pregnant or breast-feeding, or planning to become pregnant or breast-feed during protocol treatment and for 3 months after last dose of Talimogene Laherparepvec

7.0 RECRUITMENT PLAN

Investigators and their research teams will serve as the primary recruiters for this study.

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or the research team. If the investigator is a member of the treatment team, s/he will screen the patient's records for suitable research study criteria and discuss the study and the potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study. Women and minorities will be identified in this same manner.

During the initial contact between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of the patients

medical records at MSKCC to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient is ineligible for enrollment in the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

In most cases, the initial contact with the prospective subject will be by a member of the treatment team, investigator or research staff working in consultation with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of the screening log. For these reasons, we seek a (partial) limited waiver of authorization for purposes of (1) (2) handling of PHI contained within those records and provided by potential subjects; and (3) maintaining information in a screening log of patients approached (if applicable).

This limited waiver will apply only to MSKCC for the purpose of maintaining screening logs. The study will not be advertised. Subjects will not be reimbursed for participation.

We plan to accrue 18 - 34 patients at our center over 2 – 3 years.

8.0 PRETREATMENT EVALUATION

The following tests and procedures are required prior to protocol registration. These procedures are standard of care.

Within 4 weeks prior to registration

- Physical examination
- ECOG performance status
- Vital signs (weight, heart rate, blood pressure, respiratory rate, oxygen saturation) will be assessed in clinic
- Complete blood count (CBC)
- Comprehensive metabolic profile (CMP)
- Hepatitis B and C panels (Hepatitis B Surface Antigen, Hepatitis B Core Antibody (total), Hepatitis B Surface Antibody, Hepatitis C Antibody), and possible additional testing, depending on serological testing
- Prothrombin and activated partial thromboplastin time test (PT&APTT)
- Clinical review of the MSK histopathology report confirming cancer
- Quality of life assessment (Skindex-16, Appendix B) will be completed by subjects
- Pregnancy test for women of childbearing potential (by either blood or urine)
- Digital photography will be performed to document the location and size of cutaneous metastases.
- PET/CT (IV or oral contrast is not required, but is permissible if clinically indicated.)

9.0 TREATMENT/INTERVENTION PLAN

Study Assessments and Procedures

During Treatment

Weeks 0, 3, 5, 7, 11 and 15 (± 1 week)

- Physical examination
- ECOG performance status
- Vital signs (weight, heart rate, blood pressure, respiratory rate, oxygen saturation) will be assessed in clinic
- Complete blood count (CBC)
- Basic metabolic profile (BMP)
- Prothrombin and activated partial thromboplastin time test (PT&APTT)
- Pregnancy test for women of childbearing potential, by blood or urine (at weeks 3, 7, 11 and 15 only)
- Research blood test
- Research skin tumor biopsy (at weeks 0, 7 and 15 only)

Weeks 0-15 (± 1 week)

- Administration of Talimogene Laherparepvec (T-VEC)
  ** Patients with potential for clinical benefit may continue TALIMOGENE LAHERPAREPVEC after week 15 every 2 weeks for up to 24 weeks (to be determined by treating clinician)*
- Radiation therapy for patients randomized into Arm A; first fraction given 6 (+/-2) hours after week 3 Talimogene Laherparepvec administration; 2nd and 3rd fraction given every 3-6 days over next 14 days
- Adverse event review (including NCI PRO-CTCAE v1.0, Appendix C)

End of Treatment

Week 16 (± 1 week) or when TVEC is discontinued prior to week 15

- Physical examination
- ECOG performance status
- Vital signs (weight, heart rate, blood pressure, respiratory rate, oxygen saturation) will be assessed in clinic
- Adverse event review (including NCI PRO-CTCAE v1.0, Appendix C)
- Complete blood count (CBC)
- Comprehensive metabolic profile (CMP)
- Prothrombin and activated partial thromboplastin time test (PT&APTT)
- Research blood test (If TVEC stopped before week 15)
- Pregnancy test for women of childbearing potential (by either blood or urine)
- Research skin tumor biopsy (If TVEC stopped before week 15)
- Quality of life assessment (Skindex-16, Appendix B) to be completed by subjects
- Digital photography
- PET/CT (IV or oral contrast is not required, but is permissible if clinically indicated.)

Follow-Up

Week 20 (± 1 week) or 4 weeks after last TVEC dose

- Adverse event review (including NCI PRO-CTCAE v1.0, Appendix C)

9.1 Oncolytic immunotherapy by Talimogene Laherparepvec (TALIMOGENE LAHERPAREPVEC) administration

Intralesional administration of Talimogene Laherparepvec will be performed in a private room in the outpatient clinic area.

Intralesional therapy for cutaneous metastasis is a standard procedure, but Talimogene Laherparepvec is an investigational agent.

The selection of cutaneous metastasis for Talimogene Laherparepvec injection will be based on lesion size. Injections will begin with the largest metastasis, and then will proceed to the next largest metastasis, until all the cutaneous metastases have been injected, or the maximum volume of Talimogene Laherparepvec (4 mL) has been used for that treatment cycle. The injection of all of the cutaneous metastases is expected to take no more than 20 minutes.

Visceral metastases will not be injected with Talimogene Laherparepvec during the protocol therapy.

During the course of Talimogene Laherparepvec administration, patients will be clinically evaluated every 2-3 weeks (as indicated in section 10.0), for any symptoms or signs of toxicity. If a patient experiences a grade 2 or higher immune mediated adverse event, Talimogene Laherparepvec administration will be delayed until the adverse event is grade 1 or less in severity. Non-immune related adverse events grade 3 or greater will also lead to a delay in Talimogene Laherparepvec administration, until they have resolved to grade 1 or less. In the event of a dose limiting toxicity, as described in section 11.1.3, Talimogene Laherparepvec administration will be discontinued indefinitely.

9.2 External beam radiation therapy

Radiation therapy will be administered in the Department of Radiation Oncology, in a treatment suite in the outpatient clinic area. The largest cutaneous metastasis amenable to radiation therapy (see section 6.1 for criteria) will be targeted. This metastasis will also be injected with Talimogene Laherparepvec before and after radiation therapy. Other cutaneous metastases causing symptoms may also be targeted with radiation therapy at the discretion of the radiation oncologist.

Radiation therapy will be simulated prior to the initiation of radiation therapy. The patient will be positioned comfortably in a manner that facilitates the delivery of radiation therapy. Generally, this will be lying supine, recumbent on a dedicated treatment couch for radiation therapy. Immobilization equipment will be created and alignment markings generated to ensure setup reproducibility. A CT scan of the region being treated with radiation therapy will be performed with the patient in the treatment position. The simulation process takes approximately 1 hour.

Radiation therapy will be planned by delineating the grossly evident tumor (the gross tumor volume, or GTV) on the simulation CT, and creating a margin around this to account for the setup uncertainty and organ motion. An isotropic volumetric expansion of 1 cm will be performed to generate the planning target volume (PTV). The radiation dose will be prescribed so that the ≥ 95% of the PTV receives the prescription dose (27 Gy in 3 fractions over 7-9 days). Custom shielding and bolus will be created and beam type (megavoltage photons or electrons) and energy will be selected to ensure that the irradiated volume is as

small as possible, but able to deliver an adequate dose to the PTV. The irradiated skin surface receiving the prescription dose of radiation (27 Gy) will be limited to 65 cm^2 (equivalent to a round field with diameter of 9 cm, or a square field 8x8 cm). The process of target delineation and shielding creation is expected to take 20 minutes, but will be performed offline, and does require the patient to be present.

Simulation will be scheduled prior to radiation therapy.

The first dose of radiation will be delivered 6 (+/- 2) hours after the second dose of Talimogene Laherparepvec. Preclinical studies have demonstrated this sequence of therapy and interval of time is necessary to yield synergistic effects of oncolytic immunotherapy and radiotherapy. The subsequent two doses of radiation therapy will occur every 3-6 days, over no more than 14 days.

During the course of radiation therapy patients will be clinically evaluated at least once a week, for any symptoms or signs of toxicity.

9.3 Cutaneous metastasis biopsy

Punch biopsy will be obtained for immunologic correlative analyses. Local anesthesia will be provided by intradermal injection of lidocaine 1% mixed with epinephrine at 1:100,000 by a 30 gauge needle. After allowing 5 minutes for adequate anesthesia, a 3 mm punch biopsy will be obtained. The biopsy site will be closed with cuticular sutures or steri-strips. Patients will be instructed to keep the biopsy site clean after the procedure. This procedure will be done as an outpatient. The biopsy is expected to take no longer than 15 minutes and will be performed on the day of (but prior to first dose) of oncolytic immunotherapy. The biopsy will be repeated around 7 and 15 weeks after the first dose, at the site of the prior biopsy, and at up to two other sites (if present): (1) the site of another cutaneous metastasis that was not injected or irradiated (if present), (2) the site of another cutaneous metastasis that was injected but not irradiated (if present).

10.0 EVALUATION DURING TREATMENT/INTERVENTION

Study Timeline	**Pre-Treatment**	**Treatment**								**End of Treatment[6]**	**Follow-Up[7]**
Week (+/-)	**-4 to 0**	**0 (1)**	**3 (1)**	**5 (1)**	**7 (1)[4]**	**9 (1)**	**11 (1)**	**13 (1)**	**15 (1)**	**16 (1)**	**20 (1)**
Assessments											
Pathology Review	X										
PET/CT (with or without contrast)	X									X	
Quality of life questionnaires	X									X	
Digital photography	X									X	
Adverse event		X	X	X	X	X	X	X	X	X	X

review[1]											
ECOG performance status	X	X	X	X	X		X		X	X	
Vital signs (weight, heart rate, blood pressure, respiratory rate, oxygen saturation)	X	X	X	X	X		X		X	X	
Physical exam	X	X	X	X	X		X		X	X	
Complete medical history	X										
Hepatitis B Surface Antigen, Hepatitis B Core Antibody (total), hepatitis B surface Antibody, Hepatitis C Antibody[5]	X										
Comprehensive metabolic profile	X									X	
Basic metabolic profile		X	X	X	X		X		X		
Complete blood count	X	X	X	X	X		X		X		
PT&APTT	X	X	X	X	X		X		X		
Pregnancy testing (blood or urine); WOCBP only	X[2]		X		X		X		X		
Research blood test[3]		X	X	X	X		X		X		
Research skin punch biopsy[4]		X			X				X		
Treatment											
TALIMOGENE LAHERPAREPVEC		X	X	X	X	X	X	X	X†		
Radiation therapy			X*								

†Patients with potential for clinical benefit may continue TALIMOGENE LAHERPAREPVEC after week 15 every 2 weeks for up to 24 weeks (as determined bytreating clinician)
*Only for Arm A; first fraction given 6 (+/-2) hours after week 3 TALIMOGENE LAHERPAREPVEC administration; 2nd and 3rd fraction given every 3-6 days over no more than 14 days
[1]Including Appendix C, "NCI PRO-CTCAE v1.0"
[2]Within 2 weeks of starting Talimogene Laherparepvec treatment
[3] Research bloods will be 3 tubes (3 CPT) at each time point; stored at immune monitoring core facility for up to 1 year after completion of study
[4]One lavender top (EDTA) tube of blood will be drawn on the same day as the research skin punch biopsy; window for biopsywill be +/- 3 weeks
[5]Additional testing to evaluate for hepatitis maybe required depending on the serological results
[6]For patients that discontinue TVEC before week 16, the End of Treatment visit occurs after last dose of TVEC
[7]Follow-Up at week 20 or 4 weeks after last TVEC dose

11.0 TOXICITIES/SIDE EFFECTS

The study will use the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for assessing toxicity related to oncolytic immunotherapy and radiotherapy.

Overall, toxicities grade 2-5 will be identified, graded and scored using "Common Toxicity Criteria for Adverse Events, version 4.0, grading criteria and definitions".

11.1 TALIMOGENE LAHERPAREPVEC

Side effects of Talimogene Laherparepvec for cutaneous metastasis are listed below. Also see Investigators Brochure, Developmental Core Safety Information, Toxicity Management Guidelines for studies with Talimogene Laherparepvec [AMG 678] and Core Informed Consent Form Risks and Discomforts Section.

11.1.1.0 Important Identified Risks

- Disseminated herpetic infection in severely immunocompromised individuals (those with any severe congenital or acquired cellular and/or humoral immune deficiency)
- Accidental exposure of healthcare providers (HCPs) to talimogene laherparepvec
- Cellulitis at site of injection

11.1.1.1 Important Potential Risks

- Disseminated herpetic infection in immunocompromised patients (such as those with HIV/AIDS, leukemia, lymphoma, common variable immunodeficiency, or those who require high dose steroids or other immunosuppressive agents)
- Symptomatic talimogene laherparepvec infection in non-tumor tissue in treated patients
- Transmission of talimogene laherparepvec from patient to close contacts or HCPs via direct contact with injected lesions or body fluids resulting in symptomatic infection (primary or reactivation)
- Symptomatic herpetic infection due to latency and reactivation of talimogene laherparepvec or wild type HSV-1
- Immune-mediated adverse events
- Plasmacytoma at the injection site
- Impaired wound healing at the injection site
- Talimogene laherparepvec mediated anti GM-CSF antibody response

11.1.2.0 Adverse Drug Reactions (ADRs)

Adverse drug reactions observed in talimogene laherparepvec clinical trials are listed below in Table 2. Consult the current Investigator's Brochure for the full information on ADRs.

System Organ Class Preferred Term	CIOMS Frequency Very Common: ≥10% Common: 1%-<10% Uncommon: <1%
General disorders and administration site conditions	
Fatigue	Very Common
Chills	Very Common
Pyrexia	Very Common
Influenza like illness	Very Common
Malaise	Common
Axillary pain	Common
Injection site reactions*	Very Common
Gastrointestinal disorders	
Nausea	Very Common
Vomiting	Very Common
Diarrhea	Very Common
Constipation	Very Common
Abdominal pain	Common
Abdominal discomfort	Common
Musculoskeletal and connective tissue disorders	
Myalgia	Very Common
Arthralgia	Very Common
Pain in extremity	Very Common
Groin pain	Common
Skin and subcutaneous tissue disorders	
Vitiligo	Common
Rash	Common
Dermatitis	Common
Infections and infestations	
Cellulitis	Common
Oral herpes	Common
Incision site infection	Uncommon
Nervous system disorders	
Headache	Very Common
Dizziness	Common
Eye disorders	
Herpetic keratitis	Uncommon
Respiratory, thoracic and mediastinal disorders	
Oropharyngeal pain	Common
Obstructive airway disorder	Uncommon
Metabolism and nutrition disorders	
Dehydration	Common
Injury, poisoning and procedural complications	
Contusion	Common
Procedural pain	Common
Wound complication	Common
Wound secretion	Common
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	

System Organ Class Preferred Term	CIOMS Frequency Very Common: ≥10% Common: 1%-<10% Uncommon: <1%
Tumor pain	Common
Infected neoplasm	Common
Plasmacytoma at the injection site	Uncommon
Investigations	
Weight decreased	Common
Vascular disorders	
Deep vein thrombosis	Common
Flushing	Common
Blood and lymphatic system disorders	
Anemia	Common
Immune system disorders	
Worsening psoriasis	Uncommon
Pneumonitis	Uncommon
Glomerulonephritis	Uncommon
Vasculitis	Uncommon
* Injection site reactions include: very common term of injection site pain, common terms of injection site erythema, injection site hemorrhage, injection site swelling, injection site reaction, injection site inflammation, secretion discharge, injection site discharge, uncommon term of injection site warmth.	

Table 2. ADRs Observed in Talimogene Laherparepvec Clinical Trials

11.1.3.0 Dose Limiting Toxicities (DLTs)

Dose limiting toxicities (DLTs) are defined below.

11.1.3.1 Definitions of Dose Limiting Toxicity

Toxicity should be evaluated according to CTCAE version 4.0, and should only include events assessed as related to talimogene laherparepvec during treatment and up to 30 days after the last talimogene laherparepvec injection.

The following herpetic events should be considered as DLTs:

- Serious herpetic events such as herpetic encephalitis, encephalomyelitis or disseminated herpetic infection
- Any herpetic events confirmed due to talimogene laherparepvec that require treatment with acyclovir or similar anti-viral agent. Talimogene laherparepvec treatment should be suspended if treatment is required with systemic acyclovir or other anti-virals. If ongoing anti-viral treatment is required, talimogene laherparepvec treatment should be permanently discontinued

Consider also including the following as DLTs:

- Grade 3 or greater immune-mediated adverse events
- 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
- Grade 4 non-hematologic toxicity
- Grade 3 non-hematologic toxicity lasting > 3 days despite optimal supportive care
  - Grade 3 fatigue will not be classified as DLT, irrespective of duration
- Any grade 3 or higher non-hematologic laboratory value if the abnormality:
  - fails to respond to medical intervention, or
  - leads to hospitalization, or
  - persists for > 1 week unless deemed not clinically important per both investigator and sponsor
- Grade 3 or 4 febrile neutropenia
- Grade 4 thrombocytopenia associated with a bleeding event deemed at least possibly related to talimogene laherparepvec and requiring intervention
- Any other intolerable toxicity leading to permanent discontinuation of talimogene laherparepvec
- Grade 5 toxicity (ie. Death)

If an unexpected DLT deemed at least possibly related to talimogene laherparepvec occurs, talimogene laherparepvec administration should be delayed until the DLT has resolved to at least CTCAE (v. 4.0) Grade 1.

If talimogene laherparepvec dosing is delayed by more than 6 weeks from the date of the planned dose due to the occurrence of an adverse event that is considered related to talimogene laherparepvec, the subject must be permanently taken off talimogene laherparepvec treatment.

11.1.3 Dose Reductions

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. However, if in the course of administration of talimogene laherparepvec the subject cannot tolerate the full dose due to an injection-related adverse event such as pain, the total volume given should be recorded, and the reason for intolerance should be documented as an adverse event.

11.1.4 Talimogene Laherparepvec Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

If talimogene laherparepvec treatment was delayed by > 2 weeks, that dose will be deemed to have been missed and the subject will proceed to the next scheduled treatment visit. Dose reductions of talimogene laherparepvec is not permitted, other than a reduction in the volume injected due to a disease response.

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 CTCAR 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

Subjects who are receiving talimogene laherparepvec may not receive systemic antiherpetic drugs (eg, 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). If the subject requires corticosteroid dosing of > 10 mg prednisone daily (or equivalent) for related toxicities, talimogene laherparepvec dosing must be withheld until the corticosteroid dose has decreased to $\leq$ 10 mg prednisone daily (or equivalent).

Talimogene laherparepvec treatment should be continued based on the potential benefit/risk assessment of the subject. If talimogene laherparepvec dosing is delayed by more than 4 weeks from the date of the planned dose (ie, approximately 6 weeks or 7 weeks depending whether the patient is receiving Q2W or Q3W dosing from the previous dose) due to the occurrence of an adverse event that is considered related to talimogene laherparepvec, the subject must be permanently withdrawn from talimogene laherparepvec treatment.

Talimogene laherparepvec is to be permanently discontinued for subjects meeting any of the following criteria:

- The subject, for any reason, requires treatment with another anticancer therapeutic agent for treatment of the study disease. In this case, discontinuation from the treatment occurs immediately upon introduction of the new agent.
- Confirmed PD
- 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 4 weeks from the date of the planned dose (ie, approximately 6 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

- Any other talimogene laherparepvec-related non-hematologic or hematologic toxicities grade 3 or greater occur that, in the opinion of the investigator, would require a dose delay of greater than 4 weeks from the date of the planned dose (ie, approximately 6 weeks from the previous dose)
- The subject develops clinical evidence of any systemic herpes infection (such as encephalitis or disseminated infection)
- A female subject becomes pregnant or fails to use acceptable method(s) of affective contraception (for those subjects who are able to conceive)
- Concurrent medical illness that, in the judgment of the investigator, would make continued treatment with talimogene laherparepvec dangerous for the subject

For additional information related to special warnings and precautions for the use of talimogene laherparepvec, please refer to the latest version of the Investigator's Brochure.

11.2 Side effects of radiation therapy for cutaneous metastasis are listed below.

Common Terminology Criteria Adverse Event	Grade 1 frequency	Grade 2 frequency	Grade 3 frequency	Grade 4 frequency
Radiation dermatitis	100%	50%	10%	<2%
Pruritis	50%	10%		
Pain of skin	50%	10%	<2%	
Skin ulceration	50%	10%	<2%	
Alopecia	100%	10%		
Skin hyperpigmentation	50%	10%	<2%	
Skin hypopigmentation	100%	10%		
Telangiectasia	50%	10%		
Skin atrophy	100%	10%	<2%	
Skin induration	100%	10%	<2%	

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

The primary endpoint for systemic efficacy is the week 16 response of the largest metastasis not injected with Talimogene Laherparepvec or irradiated. Overall subject level response is defined as partial or complete (>50% or greater decrease in largest lesion) by the modified World Health Organization (mWHO) criteria, and will include measurements of tumor size by CT component of PET/CT, by standard uptake value (SUV) by PET component of PET/CT, and clinically by digital photography. Please see Appendix A for complete radiographic assessment details and the mWHO response criteria.

Study radiologists will be specifically informed which lesion is the target for response assessment. A separate calculation of response within and outside the irradiated volume will be determined. Study radiologists will be blinded, however, as to which treatment arm the patient has been assigned.

Radiographic imaging evaluations are considered standard of care for patients treated for cutaneous metastases.

Patients are considered evaluable for the primary endpoint if they:

- Receive one dose of Talimogene Laherparepvec, and for patients enrolled on Arm A, one dose of RT, as well as a baseline and at least one post-baseline disease assessment
- Discontinue the study due to symptomatic progression, death, or toxicity at any point, even if they have not received one dose of Talimogene Laherparepvec and one dose of RT

Patients who discontinue the study and do not meet evaluable criteria above are replaceable. In this event, the replacement patient will be assigned to the same treatment arm that lost a patient.

Patient reported health-related quality of life outcomes will be assessed using the Skindex-16 (Appendix B). The Skindex-16 is a 1 page instrument consisting of 16 items with responses provided on a 7-point Likert scale based on experience over the last week. Responses are categorized in 3 subscales: emotions, functioning, and symptoms, with combined subscale scores yielding an overall score ranging from 0 (best) to 100 (worst). Of the 16 items in the instrument, 7 contribute to symptoms, 4 contribute to emotion, and 5 contribute to functioning. In a psychometric analysis, subscales have a high degree of internal consistency reliability (Cronbach's alpha = 0.86, 0.93, 0.92 for symptoms, emotions and functioning). The subscale scores were also highly reproducible after 72 hours (r= 0.90, 0.89, and 0.88 for symptoms, emotions and functioning) (Chren MM J Cutan Med Surg 2001).

13.0 CRITERIAFOR REMOVAL FROM STUDY

Consent for participation in the study may be withdrawn by the patient or patient's health care proxy at any time.

If at any time, the patient develops clinically significant progressive disease, s/he will be withdrawn from the study and referred for alternative therapy.

If at any time the patient is found to be ineligible for the protocol as designated in the section on Criteria for Subject Eligibility (i.e., a change in diagnosis), the patient will be removed from the study.

If at any time, the protocol therapy jeopardizes the safety of the patient, s/he may be withdrawn from the study.

14.0 BIOSTATISTICS

Patients will be randomized into two separate arms (stratified by disease type), each of which will use a Simon's optimal two-stage design to assess the primary endpoint of systemic response (defined as patients achieving partial response or complete response) of a metastasis that was not injected or irradiated. The single largest measureable metastatic disease site will be used for this assessment 16 weeks after the first dose of Talimogene Laherparepvec. For each arm, a 7.5% or lower response rate is considered not promising, a 27% or higher response rate is considered promising, and the probabilities of a type I error (falsely accepting a non-promising therapy) and type II error (falsely rejecting a promising therapy) are set to 0.10 and 0.20, respectively.

In the first stage, 9 evaluable patients will be accrued to each arm. If at least 1 patient achieves response among these 9 patients, then an additional 6 patients will be accrued to that arm in the second stage. If no patients achieve response then that arm will be closed to further accrual and declared negative. At the end of the trial if 3 or more patients achieve response out of 15 then that treatment arm will be considered worthy of further investigation. This design has an early stopping probability of 0.06 if the true response rate is at least 27% and 0.50 if the true response rate is at most 7.5%. Although a comparison will be done between the two arms by a two-sample proportion test on response rates, this sample size may not have enough power to distinguish the two arms. Thus if both treatment arms are declared worthy of further investigation compared to historical control rate, the treatment arm with the higher observed response rate will be selected as the preferred treatment modality for future studies. The probabilities of selecting correctly the arm with the true higher response rate are given below. The maximum number of patients needed is 30, for which we expect to enroll in 36 months.

True response rates for the two arms	27% vs 35%	27% vs 40%	27% vs 45%	30% vs 35%	30% vs 40%	35% vs 40%	35% vs 45%	35% vs 50%
Probability of picking the correct arm (i.e., the one with the higher response rate)	0.61	0.72	0.80	0.54	0.65	0.54	0.65	0.74

Note that in the above, all patients are assumed evaluable. However, it might happen that some patients are not evaluable due to various reasons such as withdrawal or loss to follow-up, etc. Such inevaluable patients will be replaced. We expect that about 13% of patients might need to be replaced. In other words, we expect to enroll up to 34 patients in total. The clinical efficacy of Talimogene Laherparepvec will be measured by the ORR and summarized by the sample proportion for each of the two arms. A comparison will be done between the two arms. Safety of Talimogene Laherparepvec will be summarized and compared similarly. QOL total and subscale scores will be summarized numerically and graphically, and trends will be observed and reported per arm. Wilcoxon rank sum tests will also be used to compare the QOL scores between the two arms for each assessment time point. DOR will be assessed using actuarial curves based on patients who achieved response and compared between the two arms using a stratified log-rank test. Time to response onset, progression free and overall survival will be analyzed in a similar way but will be based on all patients. Immunologic response data will be summarized descriptively, with mean, median and standard deviations calculated.

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 that 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

Patients will be randomized into two separate arms (stratified by disease type). Once the participant's eligibility is established, the registration will be finalized and the participants will be randomized using the Clinical Research Database (CRDB). Randomization will be accomplished by the method of random permuted block, and will be stratified by disease type. After treatment arm is determined by randomization, RSAs at MSKCC will notify the physicians at MSKCC of the treatment arm and participant ID via email within 24 hours of randomization.

16.0 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to this study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordination of the activities of the protocol study team.

The data collected for this study will be entered into the Clinical Research Database (CRDB). Source documentation will be available to support the computerized patient record.

Data

Standardized Case Report Forms (CRFs) will not be used for this study. Data will be entered directly into the CRDB. The study RSA will ensure data is populated in the CRDB accurately 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 CRDB.

16.1 Quality Assurance

Monthly registration reports will be generated to monitor patient accrual and completeness of registration data. Routine data-quality reports will be generated to assess missing data an

inconsistencies. Accrual rates, and extent and accuracy of evaluations and follow-up, will be monitored periodically and potential problems will be brought to the attention of the study team for discussion and reaction.

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, with the first audit occurring after the 3rd patient is registered, and then more frequently if indicated. The audit will include a review of source documentation to evaluate compliance for:

- Informed consent documents and procedures
- Adherence to eligibility criteria
- Protocol defined treatment
- Required baseline, on study and follow-up protocol testing
- IRB documents (submitted amendments, annual continuing review reports, SAEs)

After the audit is complete, a summary will be sent to the PI and research team. The summarized findings will generate specific recommendations for correcting shortcomings or inadequately performed tasks. The audit report and any corrective plans will be submitted to the IRB/PB, CRQA and maintained in the department's protocol regulatory binder.

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 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data Safety and Monitoring of Clinical Trials" which can be found at:

http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines/page1

The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at:

http://smskpsps9/dept/ocrOCR%20Website%20Documents/Clinical%20Research%20Quality%20Assurance%20(CRQA)/MSKCC%20Data%20and%20Safety%20Monitoring%20Plan.pdf

There are several different mechanisms whereby clinical trials are monitored for data, safety, and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research quality assurance) and departmental procedures for quality control, plus there are 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 Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., National Institutes of Health sponsored, in-house sponsored, industrial sponsored, National Cancer

Institute cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

16.3 Regulatory Documentation

Prior to implementing this protocol at MSKCC, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MSKCC Institutional Review Board/Privacy Board (IRB/PB).

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.

16.3.2 Additional IRB Correspondence

Prospective and Retrospective Deviations

A protocol deviation Is any change or departure from an IRB approved research protocol and/or the MSK IRB Standard Operating Procedures (SOPs). Deviation may be either prospective or retrospective.

A prospective deviation is one that requires IRB approval piror to implementing the proposed change. As per IRB SOP RR-407, only specific events require a prospective deviation request. These include requests to treat a research participant who does not meet all eligibility criteria, who requires alteration in their treatment plan or requires a change in the informed consent procedures outlines in the IRB SOP.

A retrospective deviation is a deviation that has already occurred. Any retrospective deviations that do not meet the definition of an unanticipated problem must be reported to the Human Research Protection Program (HRPP) Office within 10 business days of identification by the MSK PI or study team. These deviations will be reviewed and approved by the HRPP staff and escalated to the IRB Chair/Associate Chairs, as appropriate.

16.3.3 Document Maintenance

The MSKCC 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.

A regulatory binder will be maintained at MSKCC; this binder will be electronic.

After study closure, study related documents and CRFs will be retained for 3 years.

17.0 PROTECTION OF HUMAN SUBJECTS

This protocol does not involve children, because children do not develop cutaneous metastases from melanoma, Merkel cell carcinoma or other solid malignancies often, and radiation therapy is preferable for adult patients. This statement is based on exclusion 4B of the NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects. In conformity with the NIH Revitalization Act of 1993, every effort

will be made to include participation of all ethnicities. There will be no restrictions based on racial/ethic background. The risk of participating in this protocol is related to the risk of skin injury from radiation (radiation dermatitis, pruritis, pain of skin, skin ulceration, alopecia, skin hyperpigmentation, skin hypopigmentation, telangiectasia, skin atrophy, skin induration), and/or the risk of undertreating the cutaneous metastasis. These risks are low, and the relative risk/benefit is favorable, compared with other treatment options. Alternative options for management include observation, topical or systemic chemical or immunologic therapy.

Subjects will be responsible for all charges associated with the items that are part of the routine clinical care, including diagnostic evaluations as well as the intralesional injections and radiation therapy procedures. The subjects will not be compensated for their participation. If a patient is injured as a result of being in this study, emergency care, hospitalization, and outpatient care will be made available by the hospital and billed to the patient and his/her insurance company as part of his/her medical expenses.

The exams, tests or procedures in the study are part of regular cancer care. The patient and/or health plan/insurance company will need to pay for the following tests in the study:

- Pathology review
- Physical exam
- Blood tests
- Imaging tests
- Intralesional drug administration
- Radiation therapy

17.1 Privacy

MSK'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).

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 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 signs consent. SAE reporting is required for 30-days after the participant's last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:

Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to sae@mskcc.org.

The report should contain the following information:

Fields populated from CRDB:

- Subject's initials
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject 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 PI's signature and the date it was signed are required on the completed report.

17.2.1 Sponsor Reporting

17.2.1.1 Safety Reporting to Amgen

The Sponsor/Investigator is responsible for compliance with expedited reporting requirements for serious, unexpected and related adverse events (SUSARs), for generation

of SAE reports including narratives, and for periodic reporting to Amgen of SAEs are outlined in Table 3 and Table 4 below. Individual safety reports (table 3) should be accompanied by the Fax Cover Form provided and sent to Amgen Global Safety, utilizing the fax or email information provided on the cover page. Aggregate safety reporting (table 4) including listings, tabulations and summary reports should be scanned and accompanied by the Fax Cover Form provided and sent to Amgen NASCR, utilizing the email information provided on the cover page.

In addition to the requirements outlined in Table 3 and 4 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** (refer to Section 17.2.1.2 'Accidental Exposures to Talimogene Laherparepvic and Herpetic Event Reporting').

Table 3 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
Serious Adverse Events (SAEs) (related)	Individual reports sent to Amgen at time of expedited reporting to IRB
Pregnancy/Lactation	Individual reports sent within 10 days of Sponsor/Investigator awareness

Individual reports should be faxed to 1-888-814-8653 or scanned and sent via email to svc-ags-in-us@amgen.com

Table 4. 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
US IND Annual Safety Report	Annually
Other Aggregate Analyses (any report containing safety data generated during the course of the 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

Aggregate reports should be submitted via email to the Amgen NASCR manager, accompanied by the Fax Cover Form

17.2.1.2 Accidental Exposures to Talimogene Laherparepvec and Herpetic Event Reporting

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 accident exposures to talimogene laherparepvec and for suspected herpetic events. See Table 5 below "Accidental Exposure and Herpetic Event Reporting Requirement Summary". Clinicians should review the Imlygic package insert (available online) for additional information on the safe handling of talimogene laherparepvec.

17.2.1.2.1 Accidental Exposure of HCPs to Talimogene Laherparepvec

HCPs involved in your clinical trial who were directly exposed to talimigene 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).

17.2.1.2.2 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.

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 wide 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 Contacs:**
  - 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 should 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 5. Accidental Exposure and Herpetic Event Reporting Requirement Summary

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

*The lab conducting the qPCR testing on behalf of Amgen is Viracor.

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.

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20.0 APPENDICES

Appendix A. Radiographic assessment details and the mWHO response criteria

Appendix B. Skindex-16

Appendix C. NCI PRO-CTCAE v1.0