Title: A Phase 1b/3, Multicenter, Trial of Talimogene Laherparepvec in Combination With Pembrolizumab (MK-3475) for Treatment of Unresectable Stage IIIB to IVM1c Melanoma (MASTERKEY-265)

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Amendment 4 Date:	24 January 2018
Amendment 5 Date	**15 January 2020**

Confidentiality Notice

This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures.

Investigator's Agreement

I have read the attached protocol entitled A Phase 1b/3, Multicenter, Trial of Talimogene Laherparepvec in Combination With Pembrolizumab (MK-3475) for Treatment of Unresectable Stage IIIB to IVM1c Melanoma, dated **15 January 2020**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Council for Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP) and applicable national or regional regulations/guidelines.

I agree to ensure that Financial Disclosure Statements will be completed by:

- me (including, if applicable, my spouse [or legal partner] and dependent children)
- my subinvestigators (including, if applicable, their spouses [or legal partners] and dependent children)

at the start of the study and for up to one year after the study is completed, if there are changes that affect my financial disclosure status.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

Signature

Name of Investigator

Date (DD Month YYYY)

Protocol Synopsis

Title: A Phase 1b/3, Multicenter Trial of Talimogene Laherparepvec in Combination With Pembrolizumab (MK-3475) for Treatment of Unresectable, Stage IIIB to IVM1c Melanoma

Study Phase: Phase 1b/3

Indication: Unresectable Stage IIIB to IVM1c Melanoma (American Joint Committee on Cancer [AJCC] 7th Edition)

Primary Objectives:

Phase 1b: To evaluate the safety, as assessed by incidence of dose limiting toxicity (DLT), of talimogene laherparepvec in combination with pembrolizumab in subjects with previously untreated, unresectable, stage IIIB to IVM1c melanoma.

Phase 3: To evaluate the efficacy of talimogene laherparepvec with pembrolizumab versus placebo with pembrolizumab, as assessed by progression-free survival (PFS) (response evaluation by blinded independent central review using modified Response Evaluation Criteria in Solid Tumors 1.1 [RECIST]) and overall survival (OS).

Secondary Objectives:

The secondary objectives are:

Phase 1b:

- To evaluate the efficacy of talimogene laherparepvec in combination with pembrolizumab as assessed by:
  - Confirmed objective response rate (ORR), best overall response (BOR), durable response rate (DRR), duration of response (DOR), disease control rate (DCR), and PFS (response evaluation by investigator using modified Immune-related Response Criteria [irRC])
  - OS
- To evaluate the safety of talimogene laherparepvec in combination with pembrolizumab as assessed by incidence of treatment-emergent and treatment-related adverse events (AEs), and abnormal laboratory tests.

Phase 3:

- To evaluate the efficacy of talimogene laherparepvec with pembrolizumab versus placebo with pembrolizumab, as assessed by:
  - Complete response rate (iCRR) by blinded independent central assessed modified immune-related response criteria simulating response evaluation criteria in solid tumors (modified irRC-RECIST)
  - iPFS by blinded independent central assessed modified irRC-RECIST
  - OS in subjects excluding stage IVM1c per case report form (CRF)
  - ORR, BOR, DRR, DOR, and DCR (response evaluation by blinded independent central review assessed using modified RECIST 1.1), and iORR, iBOR, iDRR, iDOR, and iDCR (response evaluation by blinded independent central review assessed using modified irRC-RECIST)
- To evaluate the safety of talimogene laherparepvec with pembrolizumab versus placebo with pembrolizumab, as assessed by incidence of treatment-emergent and treatment-related AEs, and abnormal laboratory tests.
- To evaluate patient reported outcomes (PRO) in phase 3 as assessed by the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) Global Health Status/Quality of Life (GHS/QoL) subscale.

Hypotheses:

Phase 1b:

Talimogene laherparepvec in combination with pembrolizumab will be safe and well tolerated in subjects with previously untreated, unresectable, stages IIIB to IVM1c melanoma.

Phase 3:

Two clinical hypotheses will be evaluated independently in the phase 3. The first clinical hypothesis is that talimogene laherparepvec with pembrolizumab compared to placebo with pembrolizumab will improve PFS as evaluated by blinded independent central review using modified RECIST 1.1. The second clinical hypothesis is that talimogene laherparepvec with pembrolizumab compared to placebo with pembrolizumab will improve OS.

Primary Endpoints:

Phase 1b:

- Incidence of DLT

Phase 3:

- PFS (response evaluation by blinded independent central review assessed using modified RECIST 1.1) and OS

Secondary Endpoints:

Phase 1b:

- Confirmed ORR (Complete response [CR]+partial response [PR]) (response evaluation by investigator using modified irRC)
- BOR, DRR, DOR, PFS, and DCR (response evaluation by investigator using modified irRC)
- OS
- Incidence of treatment-emergent and treatment-related AEs (all AEs, grade ≥ 3 AEs, serious adverse events, fatal AEs, AEs defined as events of interest), and abnormal laboratory tests

Phase 3:

- iCRR by blinded independent central review using modified irRC-RECIST
- iPFS by blinded independent central review using modified irRC-RECIST
- OS in subjects excluding stage IVM1c per CRF
- ORR (CR + PR), BOR, DRR, DOR, and DCR (response evaluation by blinded independent central review assessed using modified RECIST 1.1), and iORR (iCR + iPR), iBOR, iDRR, iDOR, and iDCR (response evaluation by blinded independent central review assessed using modified irRC-RECIST)
- Incidence of treatment-emergent and treatment-related AEs (all AEs, grade ≥ 3 AEs, serious adverse events, fatal AEs, and AEs defined as events of interest), and abnormal laboratory tests
- Changes in EORTC QLQ-C30 GHS/QoL subscale.

Study Design:

This is a phase 1b/3, multicenter clinical trial. The study will be conducted in 2 parts (phase 1b and phase 3) as described below.

Phase 1b:

Phase 1b is an open-label, multicenter, single-arm study. Talimogene laherparepvec will be administered in combination with pembrolizumab to approximately 20 subjects with previously untreated, unresectable, stage IIIB to IVM1c melanoma to evaluate the safety of talimogene laherparepvec in combination with pembrolizumab. In addition, phase 1b will evaluate potential blood and [redacted] that associate with response or resistance to talimogene laherparepvec in combination with pembrolizumab.

Subjects will be treated with talimogene laherparepvec in combination with pembrolizumab until 24 months from the date of the first dose of pembrolizumab or end of treatment for other reasons as described in Section 3.1.1.1, whichever occurs first.

The DLT evaluation by the dose level review team (DLRT) will be based on the initial 6 to 9 subjects meeting the DLT evaluation criteria as outlined in Section 3.1.1.1. The DLRT will recommend either to enroll more subjects for DLT evaluation in phase 1b, to prematurely stop enrollment into phase 1b, or to declare that the combination is tolerable and whether to open phase 3. However, the enrollment will not be halted while the DLT evaluation is still ongoing. Additional subjects, up to a total of approximately 20, will be enrolled in the phase 1b portion of the trial to address the secondary objective exploring the relationship between [redacted] and response to treatment. The DLRT will review additional safety data from subjects enrolled in phase 1b beyond the 6 to 9 DLT evaluable subjects to further assess the overall safety profile of talimogene laherparepvec in combination with pembrolizumab.

Phase 3:

The phase 3 study is a multicenter, double-blind, placebo-controlled, randomized trial to evaluate the efficacy, as assessed by PFS and OS of talimogene laherparepvec with pembrolizumab versus placebo with pembrolizumab in subjects with unresectable, stage IIIB to IVM1c melanoma. Approximately 660 subjects will be randomized 1:1 to receive the following:

- Arm 1: talimogene laherparepvec plus pembrolizumab
- Arm 2: placebo plus pembrolizumab

Randomization will be stratified by stage of disease: less advanced stages (IIIB, IIIC, and IVM1a) versus more advanced stages (IVM1b and IVM1c) and by prior serine/threonine protein kinase B-Raf (BRAF) inhibitor therapy: no prior BRAF inhibitor versus BRAF inhibitor with or without MEK inhibitor.

Subjects will be treated with talimogene laherparepvec in combination with pembrolizumab (arm 1) or placebo in combination with pembrolizumab (arm 2) until 24 months from the date of the first dose of pembrolizumab or end of treatment for other reasons as described in Section 3.1.2, whichever occurs first.

A Data Monitoring Committee (DMC) will be responsible to review interim safety, the ORR and DCR futility analyses, interim efficacy and futility OS analysis, and the PFS primary analysis. Planned safety monitoring will occur when approximately 20 and 100 subjects have had the opportunity to be on treatment for at least 6 weeks from the initial dosing of study treatment in phase 3 and have received at least 1 dose of study therapy and approximately every 6 months after the DMC meeting to review the futility analysis for ORR and DCR until the later of the study team's unblinding or the primary analysis of OS.

The futility analysis based on iORR and iDCR per blinded independent central review using modified irRC-RECIST is planned to include the first 160 subjects (80 per arm) that have been enrolled and have had an opportunity to be followed for the tumor assessment scheduled at week 24. Interim OS analyses are planned at the **time of the** primary analysis of PFS**,** after 282 **OS** events are observed**, and after 315 OS events are observed.** A non-binding futility analysis of OS will be conducted at the 282 OS event interim analysis if the first and second interim OS analyses do not meet their respective criterion for statistical significance. However, if 282 death events are observed prior to the 407th PFS event, then the first OS interim analysis will occur with 282 events and include a PFS interim analysis with all PFS events. In this case, the second OS interim analysis using all events will be performed at the PFS primary analysis. For more details see Section 10.4.1.4.

Safety Follow-up:

Subjects enrolled in phase 1b and phase 3 have a safety follow-up visit approximately 30 (+7) days after the last dose of all study treatment. Serious adverse events observed by the investigators or reported by the subjects that occur within 90 (+7) days after the cessation of all study treatment or 30 (+7) days following cessation of treatment if the subject initiates new

anticancer therapy, whichever is earlier, will be reported, followed, and recorded as described in Section 9.2.1.2.

Long-Term Follow-up:

Subjects enrolled in phase 1b and phase 3 will be followed for survival, subsequent anticancer therapies, and suspected injected investigational product-related AEs approximately every 12 weeks (± 28 days) for approximately 60 months after the last subjects are randomized in phase 3.

For additional information about the study design of phase 1b and phase 3, please refer to the study schema at the end of protocol synopsis and Section 3.1.

Sample Size: Approximately 680 subjects (20 subjects will enroll in phase 1b and 660 subjects will enroll in phase 3).

Summary of Subject Eligibility Criteria:

Key Inclusion Criteria –

Phase 1b and Phase 3:

Male or female age ≥ 18 years with histologically confirmed diagnosis of melanoma and stage IIIB to IVM1c for whom surgery is not recommended. Subjects must have measurable disease and be a candidate for intralesional therapy administration into cutaneous, subcutaneous, or nodal lesions. Subjects must have Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and adequate hematologic, hepatic, renal, and coagulation function.

Phase 1b only:

Subjects enrolled in phase 1b must be treatment naïve (ie, must not have received any prior systemic anticancer treatment consisting of chemotherapy, immunotherapy, or targeted therapy) given in a non-adjuvant setting for unresectable stage IIIB to IVM1c melanoma. Subjects who received prior adjuvant therapy for melanoma will not be excluded (including, but not limited to, radiotherapy, interferon, limb infusion/perfusion, or use of investigational agents in the adjuvant setting) with the exception that prior adjuvant therapy with inhibitors of programmed cell death 1 (PD-1) or programmed cell death ligand 1 (PD-L1) is not allowed. However, if the subject received adjuvant therapy, the subject must have completed therapy at least 3 months prior to enrollment.

Phase 3 only:

Subjects enrolled in phase 3 with serine/threonine protein kinase B-Raf V600 ($BRAF^{V600}$) wild-type tumors must not have received any prior systemic anticancer treatment consisting of chemotherapy, immunotherapy, or targeted therapy given in a non-adjuvant setting for unresectable stage IIIB to IVM1c melanoma. Subjects enrolled in phase 3 with $BRAF^{V600}$ mutated tumors who have received prior BRAF inhibitor therapy either alone or in combination with MEK inhibitor as their only prior systemic therapy are eligible for the phase 3 of this study. Subjects with $BRAF^{V600}$ mutant melanoma or unknown $BRAF^{V600}$ mutation status who have not received a BRAF inhibitor are also eligible for the phase 3 of this study as first-line treatment if they meet the following criteria: lactate dehydrogenase (LDH) < upper limit of normal (ULN), no clinically significant tumor related symptoms, and absence of rapidly progressing metastatic melanoma. Subjects (BRAF mutant, wildtype and UNK) who received prior adjuvant therapy for melanoma will not be excluded (including, but not limited to, interferon, ipilimumab, limb infusion/perfusion, or use of investigational agents in the adjuvant setting) with the exception that prior adjuvant therapy with inhibitors of PD-1 or PD-L1 is not allowed. However, if the subject received adjuvant therapy, the subject must have completed therapy at least 28 days prior to enrollment. Subjects must have a tumor sample (archival sample or newly obtained biopsy) that is adequate for PD-L1 assessment prior to randomization.

Key Exclusion Criteria –

Phase 1b and Phase 3:

Subjects must not have clinically active cerebral metastases and/or carcinomatous meningitis. Subjects with up to 3 cerebral metastases may be enrolled, provided that all lesions have been adequately treated with stereotactic radiation therapy, craniotomy, or Gamma Knife therapy, with no evidence of progression, and not requiring steroids, for at least 2 months prior to enrollment. Carcinomatous meningitis is excluded regardless of clinical stability. Subjects must not have primary uveal or mucosal melanoma, history or evidence of melanoma associated with immunodeficiency states (eg, hereditary immune deficiency, organ transplant, or leukemia), or history of other malignancy within the past 3 years with the exceptions of the prior malignancies noted in Section 4.1.2. Subjects may not have been previously treated with talimogene laherparepvec, any other oncolytic virus, pembrolizumab, or any other inhibitor of PD-1, PD-L1, or programmed cell death ligand 2 (PD-L2). Prior treatment with other immunotherapies (eg, anti-CD137, or cytotoxic T-lymphocyte associated antigen 4 [CTLA-4] inhibitor, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways) is allowed only in the adjuvant setting. Subjects must not have history or evidence of symptomatic autoimmune glomerulonephritis, vasculitis, other symptomatic autoimmune disease, documented history of autoimmune disease or syndrome requiring systemic treatment in the past 2 years (ie, with use of disease modifying agents, steroids or immunosuppressive agents) except vitiligo or resolved childhood asthma/atopy, or evidence of clinically significant immunosuppression. Subjects must not have active herpetic skin lesions or prior complications of herpetic infection (eg, herpetic keratitis or encephalitis) and must not require intermittent or chronic treatment with an antiherpetic drug (eg, acyclovir), other than intermittent topical use.

For a full list of eligibility criteria for phase 1b and phase 3, please refer to Section 4.1.

Investigational Product

Amgen Investigational Product Dosage and Administration:

Talimogene laherparepvec (or placebo in phase 3) will be administered by intralesional injection into injectable cutaneous, subcutaneous, and nodal lesions with or without image ultrasound guidance. Investigational product must not be administered into visceral organ metastases. See Section 6.2.1 for additional information regarding dosage and administration information.

Phase 1b:

The initial dose of talimogene laherparepvec is up to 4.0 mL of 10^6 plaque-forming units (PFU)/mL. The second dose up to 4.0 mL of 10^8 PFU/mL talimogene laherparepvec should be administered 21 (+3) days after the initial dose. Subsequent doses up to 4.0 mL of 10^8 PFU/mL talimogene laherparepvec should be given in phase 1 every 2 weeks (± 3) days until week 9 and every 3 weeks (± 3) days thereafter. When talimogene laherparepvec and pembrolizumab are administered on the same day, talimogene laherparepvec should be administered first, if possible.

Phase 3:

The initial dose of double-blind treatment is up to 4.0 mL of 10^6 PFU/mL talimogene laherparepvec or placebo (talimogene laherparepvec formulation excipients as described in the Talimogene Laherparepvec Investigator's Brochure). The second dose up to 4.0 mL of 10^8 PFU/mL talimogene laherparepvec or placebo should be administered 21 (+3) days after the initial dose. Subsequent doses up to 4.0 mL of 10^8 PFU/mL talimogene laherparepvec or placebo should be given every 2 weeks (± 3) days until week 9 and every 3 weeks (± 3) days thereafter. When double-blind treatment and pembrolizumab are administered on the same day, double-blind treatment should be administered first, if possible.

Non-Amgen Investigational Product Dosage and Administration:

Phase 1b:

Pembrolizumab at a dose of 200 mg will be administered intravenously every 2 weeks (± 3 days).

Phase 3:

Pembrolizumab at a dose of 200 mg will be administered intravenously every 3 weeks (± 3 days). The second dose of pembrolizumab will be administered 21 (+3) days after the initial dose.

See Section 6.2.2 or additional information regarding dosage and administration of pembrolizumab.

Procedures:

Screening:

Phase 1b and 3:

The following procedures are to be completed during the screening period within 28 days of enrollment/randomization (unless otherwise noted) at time points designated in the Schedule of Assessments (Table 5 and Table 6):

- Confirmation that the Informed Consent Form has been signed, followed by medical and surgical history, demographic data, vital signs, ECOG performance status, physical examination including body weight as per standard of care, and electrocardiogram (ECG)
- Local laboratory assessments: Hematology panel, chemistry panel, lactate dehydrogenase (LDH), coagulation tests, thyroid function tests, urinalysis and reflexive microscopic exam only for any abnormal urinalysis, serum or urine pregnancy test for female subjects of childbearing potential
- Clinical, radiographic, and photographic tumor assessment. Note: When a tumor lesion can be accurately evaluated by both radiographic imaging and clinical examination or photographs, radiographic imaging evaluations should be undertaken.
- Reporting of serious adverse events and documentation of concomitant medications
- Review of inclusion and exclusion criteria and registration and/or randomization in Interactive Voice Response system (IVRS).

Phase 3 only:

- Archived tumor tissue for PD-L1 expression status testing, $BRAF^{V600}$ mutation testing and [redacted] analyses.
- Biopsy for PD-L1 expression status testing, $BRAF^{V600}$ mutation testing, and [redacted] analyses: Archived tumor tissue may be substituted for newly obtained fresh biopsy, if the archival biopsy was performed within 3 months prior to day 1 of treatment, and no systemic anticancer therapies were given since the archival biopsy was done. Subjects with an unevaluable archival sample for PD-L1 expression testing and $BRAF^{V600}$ mutation testing may obtain a new biopsy. If the subject is ready to be randomized and treated after obtaining the new biopsy, randomization and start of treatment may proceed.

Treatment Procedures:

The following procedures will be completed during the treatment (at the times designated in the Schedule of Assessments (Table 5 and Table 6).

- Vital signs, physical examination, and ECOG performance status
- Local laboratory assessments: hematology panel, chemistry panel, blood sample for total IgG, thyroid function tests, coagulation tests if clinically indicated, urinalysis and reflexive microscopic exam only for any abnormal urinalysis results. Note: Additional (eg, monthly) on-treatment pregnancy testing should be conducted as required per local laws and regulations, where applicable.

[redacted]

- Clinical, radiographic, and photographic tumor assessments, and tumor response assessments using modified irRC (phase 1b) or modified irRC-RECIST (phase 3).
  Note: When a lesion can be accurately evaluated by both radiographic imaging and clinical examination or photographs, radiographic imaging evaluations should be undertaken.
- Completion of patient report outcome (PRO) questionnaires
- Reporting adverse events, serious adverse events, and pembrolizumab Events of Clinical Interest (ECI) and documentation of concomitant medications
- Administration of study treatment (refer to Section 6)

Safety Follow-up Procedures:

Upon permanent discontinuation from the study treatment for any reason, and including subjects who ended radiographic imaging or started new anticancer therapy, 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, as described in the Schedule of Assessments (Table 5 and Table 6):

- Vital signs, physical examination including body weight as per standard of care, and ECOG performance status assessment, and ECG
- Local laboratory assessments: hematology panel, chemistry panel, thyroid function tests, urinalysis and reflexive microscopic exam only for any abnormal urinalysis, serum or urine pregnancy test for female subjects of childbearing potential

[redacted]

- Clinical, radiographic, and photographic tumor assessments, and tumor response assessments using modified irRC (phase 1b) or modified irRC-RECIST (phase 3). Note: When a tumor lesion can be accurately evaluated by both radiographic imaging and clinical examination or photographs, radiographic imaging evaluations should be undertaken.
- Completion of PRO questionnaires
- Reporting of nonserious adverse events (up to safety follow-up visit), serious adverse events (within 90 [+7] days after the cessation of all study treatment or 30 (+7) days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier), and documentation of concomitant medications

Note: If an end of treatment decision occurs > 30 (+7) days after the last treatment date, then the safety follow-up visit should be performed as soon as possible (eg, within a week of the end of treatment decision).

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, initiation of additional melanoma therapy, and whether any injected investigational product-related AE has occurred. Contact for all subjects will be attempted every 12 weeks (± 28 days) following the safety follow-up visit until death, subject withdraws full consent, or up to 60 months after the end of randomization of phase 3. The sponsor may request survival status to be assessed at additional time points during the course of the study.

Clinical, radiographic, photographic tumor assessments, and tumor response assessment per modified irRC (phase 1b) or modified irRC-RECIST (phase 3) and completion of PRO questionnaires will be performed every 12 weeks (+1 week) until a documented confirmed progressive disease (PD) per modified irRC (phase 1b) or iPD per modified irRC-RECIST (phase 3), start of new anticancer treatment, death, or end of study, whichever occurs first. For subjects with progressive disease (see footnote cc of Table 6), QLQ-C30 will no longer be collected, and EuroQoL-5D-3 Level (EQ-5D-3L) will be collected through the long-term follow-up.

Blood for anti-pembrolizumab antibody and blood for PK of pembrolizumab will be collected at 3 and 6 months after study discontinuation or up until the subject starts new anticancer therapy, whichever occurs first. Antibody and PK sample collection may be discontinued if ongoing antibody and PK results from this study continue to be consistent with existing data from other pembrolizumab melanoma clinical trials.

All subjects treated with talimogene laherparepvec (all subjects in phase 1b and those who received talimogene laherparepvec in phase 3) and who permanently discontinue study will be eligible to continue follow-up for survival under an ongoing separate registry protocol that is in place for the long-term follow-up of subjects treated with talimogene laherparepvec in clinical trials. The registry protocol, including for phase 1b subjects, will not apply until the end of the study or 5 years after the last subject is enrolled in phase 3, whichever comes first. The registry protocol will also monitor for late and long-term adverse events thought to be potentially related to talimogene laherparepvec.

For a full list of study procedures, including the timing of each procedure, please refer to Section 7 and the Schedule of Assessments (Table 5 and Table 6).

Statistical Considerations:

Phase 1b:

Sample size considerations:

For phase 1b, 6 to 9 evaluable subjects will be required to assess the DLT profile of talimogene laherparepvec in combination with pembrolizumab. Additional subjects, to a total of 20, will be enrolled in the phase 1b portion of the trial to address the secondary objective exploring the relationship between [redacted] and response to treatment.

Planned method of analyses:

The efficacy and safety data will be summarized separately for phase 1b and phase 3.

The phase 1b safety analysis is planned when there are 6 to 9 DLT evaluable subjects.

For phase 1b, besides a summary of the incidence of DLTs, descriptive statistics will be provided for demographics, safety, efficacy, and [redacted] as appropriate.

Treatment effects in efficacy endpoints in phase 3 will be according to the treatment group as randomized. Frequency and percent of subjects for binary and categorical efficacy endpoints will be summarized by treatment arm. Proportions and 95% confidence interval using a normal approximation will also be provided. Treatment comparisons will be based on Cochran-Mantel-Haenszel test. Exact tests will be used for subgroup analyses when cell sizes are too small. Analysis of time-to-event endpoints will be based on K-M estimation. Hazard ratios (HRs) will be estimated using Cox proportional hazards (PH) model.

Phase 3:

Sample size considerations:

There are 2 primary endpoints, PFS and OS, in phase 3. The hypothesized reduction of 1/3 hazard for PFS (talimogene laherparepvec and pembrolizumab / pembrolizumab and placebo) is equivalent to an HR of 0.67 and the hypothesized HR for OS is 0.70. Initial allocation of significance level, overall 2-sided 0.05, is 2-sided 0.005 for PFS and 2-sided 0.045 for OS. The event goal for PFS to achieve 90% power at 2-sided 0.005 is 407. The event goal for OS adjusted for 4 group sequential analyses to achieve 90% power at a 2-sided 0.045 is 346. The sample size is 660 subjects (ie, 330 per arm) based on an estimate of 346 death events occurring within 5 years (60 months).

Planned method of analyses:

The primary analysis of PFS will be based on tumor assessments per the blinded independent central review using modified RECIST 1.1. For analyses of the 2 primary endpoints PFS and OS, a stratified log-rank test will be used as the primary method for testing the null hypothesis of no treatment difference. The stratification factors will include randomization factors per IVRS and PD-L1 status at baseline (positive vs not positive). Hazard ratios will be estimated using the Cox proportional hazards (PH) model stratified by randomization factors per IVRS and the baseline PD-L1 status (positive vs not positive). Multiple statistical testing for the dual primary endpoints

and the 3 secondary endpoints of iCRR, iPFS, and OS in subjects excluding disease stage IVM1c will follow a graphic-based, multiple group sequential hypotheses testing procedure (Maurer and Bretz, 2013) to ensure a strong control of an overall Type I error of 0.05 (see Section 10.5). The information fraction will be based on the number of events included in the respective analysis for all time to event endpoints, and it will be based on the number of subjects with potential follow-up of at least 36 weeks for iCRR. The nominal alpha will be transitioned to test hypotheses for the 3 secondary endpoints if either the primary endpoint of PFS or OS is statistically significant.

Two interim safety analyses are planned to evaluate the safety of talimogene laherparepvec in combination with pembrolizumab in the target population for the phase 3. Planned safety monitoring will occur when approximately 20 and 100 total subjects, respectively, have had the opportunity to be on treatment for at least 6 weeks from the initial dosing of study treatment in phase 3 and have received at least 1 dose of study therapy.

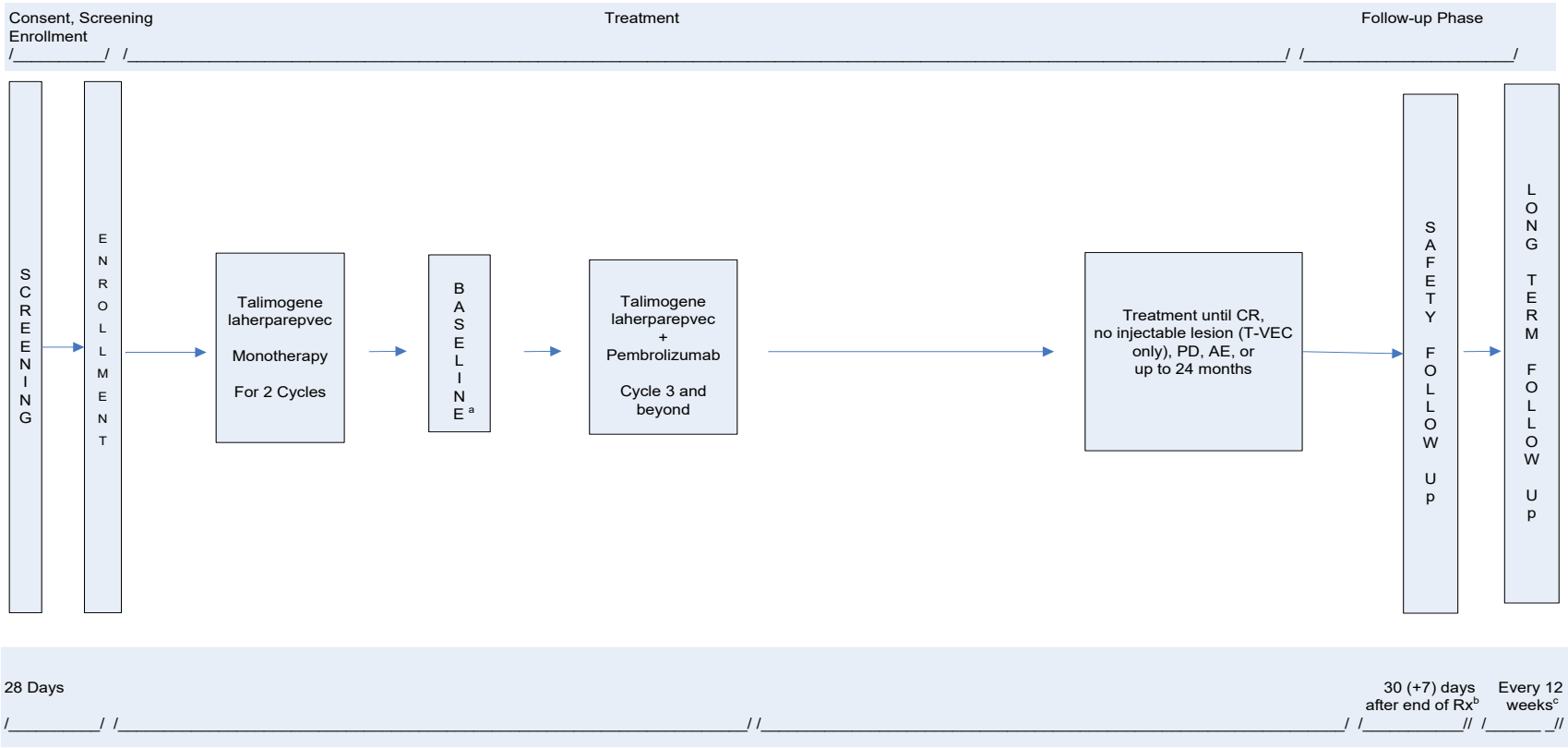
The Bayesian method will be used for the futility analysis when assessing iORR and iDCR by blinded independent central review using modified irRC-RECIST. The iORR futility criterion will be a posterior probability < 0.65 of at least a 6% absolute iORR increase (pembrolizumab and talimogene laherparepvec arm – placebo plus pembrolizumab arm), and the iDCR futility criterion will be a posterior probability < 0.75 of at least a 10% absolute DCR increase. The interim futility analysis will be reviewed by the DMC, and the DMC will declare the combination therapy futile if both the iORR and iDCR futility criteria are met; however, the DMC's recommendation will be non-binding and therefore the sponsor will make the final decision to terminate the study prematurely.

At the time of the PFS primary analysis, an interim efficacy OS analysis will be performed. **The** second interim OS analysis is planned after 282 events for efficacy and futility. The interim OS futility analysis will be non-binding and define futility as a conditional power < 10% assuming a constant treatment effect; however, futility will also be similarly defined by considering a possible non-constant treatment effect that increases over time. The order for the event-driven OS interim and PFS primary analyses may not be as anticipated due to incorrect design assumptions. If 282 OS events are observed prior to 407 PFS events, the first event-driven analysis will be an OS interim with 282 OS events and a PFS interim using all events. **The third interim OS analysis for efficacy is planned after 315 events are observed.**

The remaining secondary endpoints of ORR, iORR, DCR, iDCR, DRR, and iDRR will be summarized by treatment arm with associated 95% CI. DOR and iDOR among responders will be estimated by treatment group using the Kaplan-Meier method. Analyses of response endpoints will be performed first according to the blinded independent central review assessment using modified RECIST and modified irRC-RECIST, respectively. Following the intent-to-treat principle, subjects who do not have any follow up tumor assessments will be determined as non-completeresponders. Analysis for the PRO related endpoints will be descriptive. Safety data including laboratory test results, vital signs and treatment-emergent adverse events will be summarized by treatment arms.

[redacted] The analyses of exploratory PRO endpoints are described in Section 10.5.5. For a full description of statistical analysis methods, please refer to Section 10.

Phase 1b Study Design and Treatment Schema



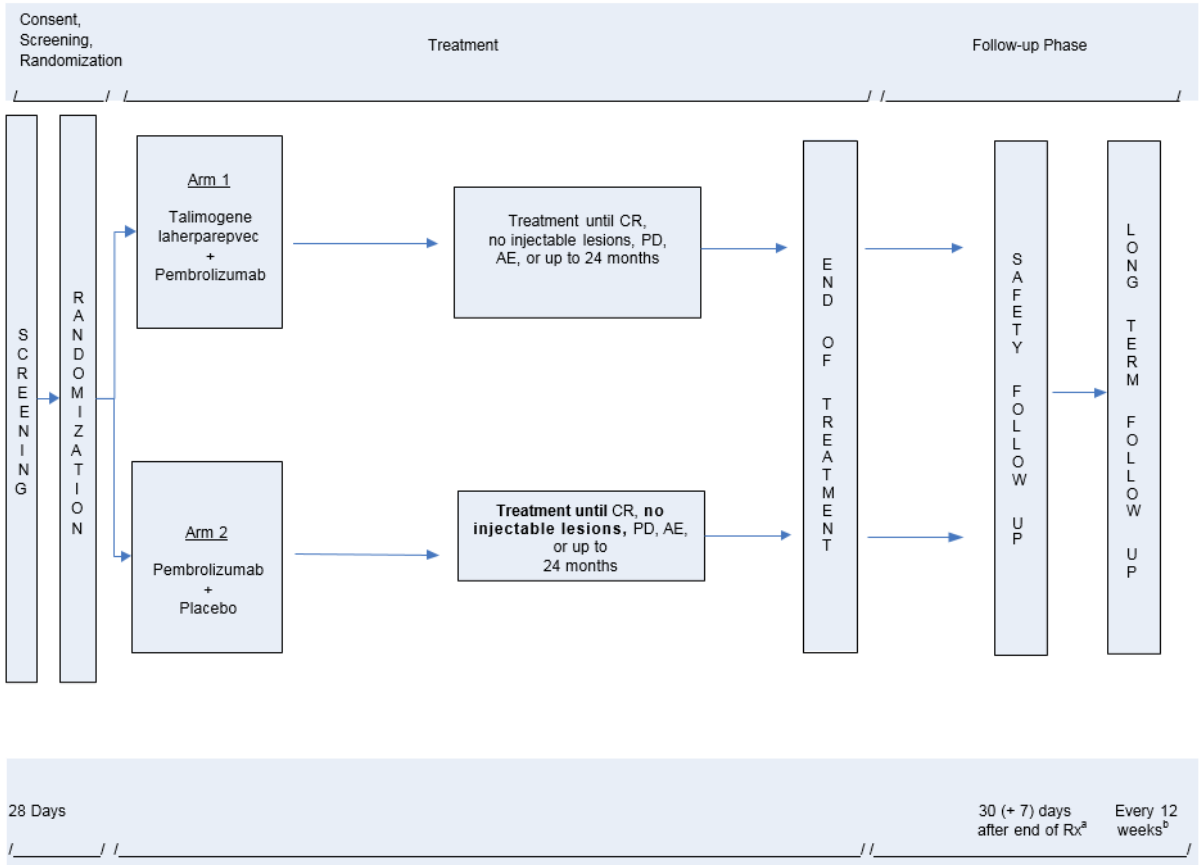
AE = adverse event requiring permanent discontinuation of study treatment; CR = complete response; PD = progressive disease; Rx = treatment; T-VEC = talimogene laherparepvec

[a] Subject will undergo clinical, photographic, and radiographic tumor assessments after 2 cycles of talimogene laherparepvec and prior to start of pembrolizumab.

[b] Subjects will be followed up for SAEs until 90 (+ 7) days after the last dose of talimogene laherparepvec or the last dose of pembrolizumab, whichever is later.

[c] Long-term follow-up every 12 weeks (± 28 days) until approximately 60 months after last subject enrolled in phase 3.

Phase 3 Study Design and Treatment Schema



AE = adverse event requiring permanent discontinuation of study treatment; CR = complete response; PD = progressive disease; Rx = treatment; T-VEC = talimogene laherparepvec

[a] Subjects will be followed up for SAEs until 90 (+ 7) days after the last dose of talimogene laherparepvec or the last dose of pembrolizumab, whichever is later.

[b] Long-term follow-up every 12 weeks (± 28 days) until approximately 60 months after last subject enrolled in phase 3.

Study Glossary

Abbreviation or Term	Definition/Explanation
AE	adverse event
AJCC	American Joint Committee on Cancer
ANC	absolute neutrophil count
ANOVA	analysis of variance
ALT	alanine aminotransferase
AST	aspartate aminotransferase
$BRAF^{V600}$	serine/threonine protein kinase B-Raf V600
BOR	best overall response
BUN	blood urea nitrogen
CI	confidence interval
CRF	case report form
CNS	central nervous system
CR	complete response
CRR	complete response rate
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte associated antigen 4
DCR	disease control rate
DILI	drug-induced liver injury
DLRT	Dose Level Review Team
DLT	dose limiting toxicity
DMC	Data Monitoring Committee
DOR	duration of response
DRR	durable response rate
ECG	electrocardiogram
ECI	events of clinical interest
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
End of Follow-up	defined as when the last subject completes the last protocol-specified safety or long-term follow-up assessment in the study, whichever is later
End of Study for Individual Subject	defined as the last day that protocol-specified procedures are conducted for an individual subject

Abbreviation or Term	Definition/Explanation
End of Study (primary completion)	defined as the date when the last subject is assessed or receives an intervention for the primary endpoint(s), for the purpose of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early.
End of Study (end of trial)	defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable.
End of Treatment	defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D-3L	EuroQoL-5D-3 Level
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
FT4	free thyroxine
GCP	Good Clinical Practice
GHS	Global Health Status
GM-CSF	granulocyte macrophage colony-stimulating factor
GMI	Growth Modulation Index
H	hypothesis
HR	hazard ratio
HSU	health state utility
HSV, HSV-1	herpes simplex virus, herpes simplex virus type 1
iBOR	best overall response (by modified irRC-RECIST)
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
iCR	complete response (by modified irRC-RECIST)
iCRR	complete response rate (by modified irRC-RECIST)
iDCR	disease control rate (by modified irRC-RECIST)
iDOR	duration of response (by modified irRC-RECIST)
iDRR	durable response rate (by modified irRC-RECIST)
ILD	interstitial lung disease
INR	international normalization ratio
iORR	objective response rate (by modified irRC-RECIST)
iPD	progressive disease (by modified irRC-RECIST)
iPFS	progression-free survival (by modified irRC-RECIST)
IPIM	Investigational Product Instruction Manual
iPR	partial response (by modified irRC-RECIST)

Abbreviation or Term	Definition/Explanation
irAE	immune-related adverse event
IRB/IEC	institutional review board/independent ethics committee
irRC	Immune-related Response Criteria
irRC-RECIST	Immune-related Response Criteria (irRC) simulating Response Evaluation Criteria in Solid Tumors (RECIST)
iSD	stable disease (by modified irRC-RECIST)
iUE	unevaluable (by modified irRC-RECIST)
Interactive Voice Response (IVR)	telecommunication technology that is linked to a central computer in real time as an interface to collect and process information.
KM	Kaplan-Meier
LDH	lactate dehydrogenase
mAb	monoclonal antibody
MRI	magnetic resonance imaging
mOS	**median overall survival**
MPR	minor partial response
MTD	maximum tolerated dose
NSAID	non-steroidal anti-inflammatory drug
NSCLC	non small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death-1
PD-L1	programmed cell death-1 ligand 1
PD-L2	programmed cell death-1 ligand 2
PET	positron emission tomography
PES	polyethersulfone
PFS	progression-free survival
PFU	plaque-forming unit
PK	pharmacokinetics
PR	partial response
PRO	patient reported outcome
PT	prothrombin time
PTT/aPTT	partial thromboplastin time/activated partial thromboplastin time
Q2W	every 2 weeks
Q3W	every 3 weeks
QoL	quality of life

Abbreviation or Term	Definition/Explanation
QLQ-C30	Quality of Life Questionnaire Core 30
qPCR	real-time polymerase chain reaction
RECIST	Response Evaluation Criteria in Solid Tumor
RBC	red blood cell
SAE	serious adverse event
SD	stable disease
Source Data	information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline [E6]). Examples of source data include subject identification, randomization identification, and stratification value.
SPD	the sum of the products of the two largest perpendicular diameters
Study Day 1	defined as the first day that protocol-specified investigational product(s)/protocol required therapies is/are administered to the subject
T3	triiodothyronine
TID	Trial Integrity Document
TSH	thyroid stimulating hormone
ULN	upper limit of normal
UE	unevaluable
USA	United States of America
VAS	visual analogue scale
[redacted]	
WBC	white blood cell

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1. OBJECTIVES

1.1 Primary

The primary objectives are:

Primary Objectives:

Phase 1b:

- To evaluate the safety, as assessed by incidence of dose limiting toxicity (DLT), of talimogene laherparepvec in combination with pembrolizumab in subjects with previously untreated, unresectable, stage IIIB to IVM1c melanoma.

Phase 3:

- To evaluate the efficacy of talimogene laherparepvec with pembrolizumab versus placebo with pembrolizumab, as assessed by progression-free survival (PFS) (response evaluation by blinded independent central review using modified Response Evaluation Criteria in Solid Tumors [RECIST] 1.1) and overall survival (OS).

1.2 Secondary

The secondary objectives are:

Phase 1b:

- To evaluate the efficacy of talimogene laherparepvec in combination with pembrolizumab as assessed by:
  - Confirmed objective response rate (ORR), best overall response (BOR), durable response rate (DRR), duration of response (DOR), disease control rate (DCR), and PFS (response evaluation by investigator using modified immune-related Response Criteria [irRC])
  - OS
- To evaluate the safety of talimogene laherparepvec in combination with pembrolizumab as assessed by incidence of treatment-emergent and treatment-related adverse events, and abnormal laboratory tests.

Phase 3:

- To evaluate the efficacy of talimogene laherparepvec with pembrolizumab versus placebo with pembrolizumab, as assessed by:
  - Complete response rate (iCRR) by blinded independent central assessed modified immune-related response criteria simulating response evaluation criteria in solid tumors (modified irRC-RECIST)
  - iPFS by blinded independent central assessed modified irRC-RECIST
  - OS in subjects excluding stage IVM1c per case report form (CRF)
  - ORR, BOR, DRR, DOR, and DCR (response evaluation by blinded independent central review assessed using modified RECIST 1.1), and iORR, iBOR, iDRR, iDOR, and iDCR by blinded independent central review assessed using modified irRC-RECIST)

- To evaluate the safety of talimogene laherparepvec with pembrolizumab versus placebo with pembrolizumab, as assessed by incidence of treatment-emergent and treatment-related adverse events, and abnormal laboratory tests.
- To evaluate patient reported outcomes (PRO) in phase 3 as assessed by the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) Global Health Status/Quality of Life (GHS/QoL) subscale.

1.3 Exploratory

The exploratory objectives are:

Phase 1b:

- To evaluate whether talimogene laherparepvec induces changes in PD-L1 expression by immunohistochemistry (eg, negative to positive) in injected and non-injected lesions after starting talimogene laherparepvec in subjects whose tumors are PD-L1-negative prior to receiving talimogene laherparepvec in phase 1b.

[redacted]

Phase 3:

- iORR, iBOR, iDRR, iDOR, iDCR, and iPFS (response evaluation by investigator-assessed modified irRC-RECIST).

[redacted]

- To evaluate the incidence of anti-pembrolizumab antibodies when pembrolizumab is administered in combination with talimogene laherparepvec or placebo.
- To evaluate the pharmacokinetics (PK) of pembrolizumab when administered in combination with talimogene laherparepvec or placebo.
- To evaluate PROs as assessed by the EORTC QLQ-C30 subscales.
- To estimate health state utility (HSU) values using the EuroQoL-5D-3 Level (EQ-5D-3L).

[redacted]

2. BACKGROUND AND RATIONALE

2.1 Melanoma and Programmed Cell Death 1 (PD-1) Receptor Inhibitor

In adults, cutaneous melanoma is the fifth most common cancer in men and the seventh most common cancer in women in the United States of America (USA), with an estimated 76,100 new cases and 9,710 deaths expected in 2014 (Siegel et al, 2014). In Europe, the annual incidence of melanoma is somewhat lower than that in the USA, with a crude rate of approximately 13.5 per 100,000 as compared with 21.9 per 100,000 in the USA, but is the seventh most common cancer among women (Ferlay et al, 2013; Siegel et al, 2014). In Europe as a whole, approximately 100,442 new cases were diagnosed in 2012 (Ferlay et al, 2013). The incidence of melanoma is increasing rapidly worldwide, with a 270% increase in the USA between 1973 and 2002. This increase is the most rapid of any cancer with the exception of lung cancer in women (Jemal et al, 2006; Ries et al, 2000).

Cancer has developed multiple mechanisms to successfully avoid recognition by the immune-system and resultant antitumor effector functions, thus limiting the benefits of cancer immunotherapies (Whiteside, 2006). Therapeutic strategies have recently been developed to overcome a tumor's ability to protect itself from targeted immune response. Antibodies that block the inhibitory receptor cytotoxic T-lymphocyte associated antigen 4 (CTLA-4), such as ipilimumab, have been shown to release one of these negative immune regulatory pathways, leading to durable responses in a subgroup of patients with metastatic melanoma and an OS benefit in patients with metastatic melanoma (Robert et al, 2011; Hodi et al, 2010).

The programmed cell death-1 (PD-1) receptor is another inhibitory receptor expressed by T cells. Its primary ligand, programmed cell death-1 ligand 1 (PD-L1), is frequently expressed within the tumor microenvironment, including cancer cells and tumor-infiltrating macrophages. The PD-1 receptor has a second ligand, programmed cell death-1 ligand 2 (PD-L2), which is preferentially expressed by antigen-presenting cells (Pardoll, 2012). In tumor models, PD-1 negatively regulates the effector phase of T-cell responses after ligation of PD-L1 expressed by the tumor (Blank et al, 2004). It has been postulated that antibodies that block the interaction between PD-1 and PD-L1 in tumors may preferentially release the cytotoxic function of tumor-specific T cells with fewer systemic toxic effects than those that are seen with other immune checkpoint inhibitors (Pardoll, 2012; Ribas; 2012; Okazaki and Honjo, 2007). Inhibitory antibodies targeted to PD-1 and PD-L1 have demonstrated objective responses in

multiple tumor types including melanoma (Robert et al, 2015; Hamid et al, 2013; Brahmer et al, 2012; Topalian et al, 2012). **Anti-PD-1 antibodies have also been shown to improve overall survival in melanoma (Larkin et al, 2019; Robert et al, 2019).** The combination of PD-1 blockade with nivolumab and CTLA-4 blockade with ipilimumab has resulted in **significantly** longer progression free survival **and overall survival** than **ipilimumab** but was associated with a high rate of grade 3 or 4 adverse events (**Larkin et al, 2019;** Larkin et al, 2015).

2.2 Talimogene Laherparepvec Background

Talimogene laherparepvec is an intralesionally delivered oncolytic immunotherapy comprised of a genetically engineered herpes simplex virus type 1 (HSV-1) that selectively replicates in tumor tissue (Talimogene Laherparepvec Investigator's Brochure). The genes encoding neurovirulence factor ICP34.5 and ICP47 are functionally deleted in the virus, while the gene for human granulocyte macrophage colony-stimulating factor (GM-CSF) is inserted.

The ICP34.5 functional deletion allows the virus to replicate selectively in tumors. The deletion of ICP47 prevents its function of blocking the transporter associated with antigen processing 1 and 2 and subsequent antigen presentation on major histocompatibility complexes I and II. ICP47 deletion also allows the increased expression of the US11 gene, which promotes virus growth in cancer cells without decreasing tumor selectivity. Additionally, the virus contains the coding sequence for human GM-CSF, a pleiotropic cytokine involved in the stimulation of cellular immune responses.

In the open-label, randomized, phase 3 study of talimogene laherparepvec versus subcutaneously administered GM-CSF in stage IIIB, IIIC, and IV unresectable melanoma, talimogene laherparepvec or GM-CSF was administered until complete response (CR), clinically significant PD, intolerable side effects, 12 months of therapy without an objective response, or withdrawal of consent (OPTiM study, Study 005-05). The primary endpoint of the study was DRR, defined as the rate among subjects with an objective response (CR or partial response [PR]) lasting continuously for 6 months and starting any time within 12 months of initiating therapy. Primary analysis of the OPTiM study showed a statistically significant difference between the rate of durable response among subjects treated with talimogene laherparepvec (16%; 95% confidence interval [CI]: 12%, 21%) versus those treated with GM-CSF (2%; 95% CI: 0%, 5%) (p-value < 0.0001). Responses were seen in injected, non-injected, and visceral lesions. A

difference in the secondary endpoint of OS was also seen with a hazard ratio (HR) of 0.79 (95% CI: 0.62-1.00), p = 0.051. Median OS of subjects treated with talimogene laherparepvec was 4.4 months longer than those treated with GM-CSF (23.3 months for talimogene laherparepvec versus 18.9 months for GM-CSF) (Kaufman et al, 2014). Survival at 1, 2, 3, and 4 years in the talimogene laherparepvec arm was estimated to be 74%, 50%, 39% and 33%, respectively, and 69%, 40%, 30% and 21% in the GM-CSF arm, respectively. Median (range) time to response among the 78 subjects in the talimogene laherparepvec arm with a response was 4.1 (1.2 to 16.7) months, whereas among the 8 in the GM-CSF arm with a response, it was 3.7 (1.9 to 9.1) months. Fifty-four percent of talimogene laherparepvec objective responders and 48% of talimogene laherparepvec durable responders exhibited “interval progression”, which is transient locoregional or distant progression including appearance of new lesions, before ultimately achieving response (Ross et al, 2014; Kaufman et al, 2013). Subjects with HSV-1 seronegative or seropositive status at baseline had similar ORR (23.7 vs 28.6%), DRR (13.4 vs 17.7%, respectively), and OS HR ratio (0.79 vs 0.81) with talimogene laherparepvec (Kaufman et al, 2014; Andtbacka et al, 2013; data on file). 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%) (all treatment-emergent). 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, 8 were attributable to disease progression. The remaining 2 fatal adverse events (sepsis in the setting of salmonella infection; myocardial infarction) were not considered treatment-related per investigator (Andtbacka et al, 2013). Subjects with HSV-1 seronegative or seropositive status at baseline had similar incidence of grade 3 and 4 (20.4 vs 17.7%) and serious adverse events (25.5 vs 28.0%) on talimogene laherparepvec (Andtbacka et al, 2013; data on file).

The combination of talimogene laherparepvec with ipilimumab, an immune checkpoint inhibitor, for the treatment of subjects with unresected stage IIIB-IV melanoma is currently being evaluated in the ongoing 20110264 phase 1b/2 study. The phase 1b portion of this study enrolled 19 treatment naïve patients of whom 18 were treated with the combination of both talimogene laherparepvec and ipilimumab (Puzanov et al, 2014). One subject withdrew consent after one dose of talimogene laherparepvec. There were

no reported DLT during the DLT evaluation period (6 weeks following the first administration of ipilimumab). The most common adverse events were chills, fatigue, and pyrexia occurring in 11 subjects (58%) each. Grade 3 or 4 adverse events of any kind occurred in 6 subjects (32%). The only grade 3 or 4 adverse event occurring in more than one subject was grade 3 nausea in two subjects. Two subjects (11%) experienced possible immune-related grade 3 or 4 adverse events attributed either ipilimumab or the combination of ipilimumab and talimogene laherparepvec. There were no unexpected adverse events attributable to the combination therapy that have not been seen previously with either ipilimumab or talimogene laherparepvec individually. Of the subjects who experienced possible immune-related grade 3 or 4 adverse event, 1 subject experienced grade 3 hypophysitis attributed to ipilimumab and grade 3 adrenal insufficiency and grade 3 diarrhea, both of which were attributed to the combination of products. The other subject experienced grade 4 amylase and lipase elevations which were attributed to ipilimumab. These grade 3/4 adverse event rates and possible immune-related adverse event are consistent with what has been reported with ipilimumab alone (Hodi et al, 2010). One grade 5 adverse event of metastases to the central nervous system occurred during the treatment and safety follow-up period. Analysis performed at a median tumor follow-up time of 15.6 months revealed 9 objective responses (50%) with 4 confirmed CRs (33%) and DRR 44% by irRC (Puzanov et al, 2015). Median PFS was not yet reached with 50% of patients still without progression at 18 months. Median OS was not yet reached with 67% of patients still alive at 18 months. Median time to response was 4.1 months, and median duration of treatment was 13.3 weeks. Phase 2 of the study is currently ongoing. Primary analysis of the phase 2 portion of the study was recently reported (Chesney et al, 2017). 198 patients were randomized: 98 in the talimogene laherparepvec + ipilimumab arm and 100 in the ipilimumab arm. Baseline characteristics were generally balanced between the 2 arms. Thirty eight patients (39%) in the combination arm and 18 patients (18%) in the ipilimumab arm had an objective response (odds ratio, 2.9; 95% CI: 1.5 to 5.5; p = 0.002). Responses were not limited to injected lesions. Visceral lesion decreases were observed in 51 patients (52%) in the combination arm and 23 patients (23%) in the ipilimumab arm. Of 183 patients in the safety set (93 in the combination arm and 90 in the ipilimumab arm), the incidences of grade 3/4 treatment related adverse events were 45% in the combination arm and 35% in the ipilimumab arm. The most frequently occurring adverse events included fatigue (combination: 59%, ipilimumab: 42% respectively), chills (53%, 3%), diarrhea (42%, 35%), pruritus (40%,

36%), rash (39%, 28%) and nausea (38%, 24%). Three patients in the combination arm had fatal adverse events that were not treatment related.

Refer to the Talimogene Laherparepvec Investigator's Brochure for additional information related to safety and efficacy of talimogene laherparepvec (Talimogene Laherparepvec Investigator's Brochure).

2.3 Pembrolizumab Background

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the PD 1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD 1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous immunotherapy for advanced malignancies. Keytruda™ (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the Investigator brochure (Pembrolizumab Investigator's Brochure).

A phase 3 registration trial (KEYNOTE-006) of pembrolizumab versus ipilimumab in ipilimumab-naive subjects with advanced melanoma has been published (clinicaltrials.gov identifier NCT01866319, Schachter et al, 2007). This is a 3-arm study to evaluate the safety and efficacy of two dosing schedules of pembrolizumab compared to ipilimumab for the treatment of ipilimumab-naïve participants with unresectable or metastatic melanoma. Subjects are randomized 1:1:1 to receive pembrolizumab 10 mg/kg every 2 weeks for up to 2 years or pembrolizumab 10 mg/kg every 3 weeks for up to 2 years or ipilimumab 3 mg/kg for a total of 4 doses. Primary endpoints of this study are progression free survival (PFS) and overall survival (OS). At an interim analysis with 834 subjects enrolled and median duration of follow-up 7.9 months (range 6.1-11.5 months), the response rate for pembrolizumab every 2 weeks was 33.7% and every 3 weeks was 32.9% as compared with ipilimumab at 11.9% ($p < 0.001$ for both comparisons) (Robert et al, 2015). The PFS hazard ratio was 0.58 ($P < 0.001$ for both pembrolizumab regimens versus ipilimumab), and the hazard ratio for death for pembrolizumab every 2 weeks was 0.63 ($P = 0.0005$) and 0.69 for pembrolizumab every 3 weeks ($P = 0.0036$) versus ipilimumab. Rates of treatment-related adverse events of grade 3 to 5 were lower in the pembrolizumab groups (13.3% and 10.1%) than in the ipilimumab group (19.9%) (Robert et al, 2015). **The overall survival benefit of pembrolizumab versus ipilimumab continued to hold after a median follow-up of 57.7 months (range 56.7 to 59.2 months). The median overall survival (mOS) was**

32.7 months in the combined pembrolizumab groups and 15.9 months in the ipilimumab group (hazard ratio = 0.73, 95% confidence interval of 0.61 to 0.88, P = 0.00049) (Robert et al, 2019).

The dose of pembrolizumab planned to be studied in this trial is 200 mg, as approved in the United States. Information on the rationale for selecting 200 mg every 3 weeks in the phase3 part of this trial is summarized below.

KEYNOTE-001 is an open-label Phase I study conducted to evaluate the safety, tolerability, PK and pharmacodynamics, and anti-tumor activity of pembrolizumab when administered as monotherapy. The dose escalation portion of this trial evaluated 3 dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) and dose expansion cohorts evaluated 2 mg/kg every 3 weeks (Q3W) and 10 mg/kg Q3W in subjects with advanced solid tumors. All dose levels were well tolerated and no dose-limiting toxicities were observed. This first-in-human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels. No maximum tolerated dose (MTD) has been identified. In addition, 2 randomized cohort evaluations of melanoma subjects receiving pembrolizumab at a dose of 2 mg/kg versus 10 mg/kg Q3W have been completed, and 1 randomized cohort evaluating 10 mg/kg Q3W versus 10 mg/kg Q2W has also been completed. The clinical efficacy and safety data demonstrate a lack of important differences in efficacy or safety profile across doses.

An integrated body of evidence suggests that 200 mg Q3W is expected to provide similar response to 2 mg/kg Q3W, 10 mg/kg Q3W, and 10 mg/kg Q2W. Previously, a flat pembrolizumab exposure-response relationship for efficacy and safety has been found in subjects with melanoma in the range of doses between 2 mg/kg and 10 mg/kg. Exposures for 200 mg Q3W are expected to lie within this range and will be close to those obtained with 2 mg/kg Q3W dose.

A population PK model, which characterized the influence of body weight and other patient covariates on exposure, has been developed. The PK profile of pembrolizumab is consistent with that of other humanized monoclonal antibodies, which typically have a low clearance and a limited volume of distribution. The distribution of exposures from the 200 mg fixed dose are predicted to considerably overlap those obtained with the 2 mg/kg dose and importantly will maintain individual patient exposures within the exposure range established in melanoma as associated with maximal clinical response. Pharmacokinetic properties of pembrolizumab, and specifically the weight-dependency

in clearance and volume of distribution are consistent with no meaningful advantage to weight-based dosing relative to fixed dosing.

In translating to other tumor indications, similarly flat exposure-response relationships for efficacy and safety as observed in subjects with melanoma can be expected, as the anti-tumor effect of pembrolizumab is driven through immune system activation rather than through a direct interaction with tumor cells, rendering it independent of the specific tumor type. In addition, available PK results in subjects with melanoma, non small cell lung cancer (NSCLC), and other tumor types support a lack of meaningful difference in PK exposures obtained at tested doses among tumor types. Thus, the 200 mg Q3W fixed-dose regimen is considered an appropriate fixed dose for other tumor indications as well. A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage. The existing data suggest 200 mg Q3W as the appropriate dose for pembrolizumab.

2.4 Rationale for Combination Therapy of Talimogene Laherparepvec and Pembrolizumab

Talimogene laherparepvec and PD-1 blockade likely play complementary roles in regulating adaptive immunity. Talimogene laherparepvec likely augments dendritic cell-mediated tumor antigen presentation through local expression of GM-CSF (Kaufman et al, 2010) and local antigen release by direct tumor lysis. Pembrolizumab prevents T-cell exhaustion in peripheral tissues. The combination of an agent that increases tumor-specific immune activation with one that blocks inhibitory T-cell checkpoints could produce greater antitumor activity than either agent alone. Talimogene laherparepvec combined with ipilimumab in a phase 1b study demonstrated response rates of 50% by irRC with 22% confirmed CR and was tolerable with no unexpected adverse events (AEs) (Puzanov et al, 2015).

A prior concurrent regimen of nivolumab, a PD-1 inhibitor, with ipilimumab, a CTLA-4 inhibitor has yielded higher response rates (57.5%, 95% CI 52.0 to 63.2) and median progression free survival (11.5 months, 95% CI 8.9 to 16.7) in advanced melanoma than **ipilimumab** (Larkin et al, 2015)**. Updated results also showed a longer mOS for the combination (mOS > 60 months) versus ipilimumab (mOS = 19.9 months) (Larkin et al, 2019),** suggesting that immune therapies can be given concurrently to improve efficacy. However, toxicity was also increased with 55% having grade 3 or 4 adverse events for combination versus 16.3% for nivolumab and 27.3% for ipilimumab.

As both pembrolizumab and talimogene laherparepvec have had relatively low toxicity as single agents, it is possible that the overall incidence of severe adverse events would remain low when they are combined as has been seen with the talimogene laherparepvec and ipilimumab combination.

This phase 1b/3, multicenter, study is intended to provide confirmation that a regimen of an oncolytic immunotherapy (talimogene laherparepvec) and an immune checkpoint inhibitor (pembrolizumab) is safe and tolerable, and that the combination treatment might enhance the clinical efficacy shown when pembrolizumab is administered alone to subjects with unresectable, stage IIIB to IVM1c melanoma.

As this is the first use of talimogene laherparepvec with pembrolizumab, the phase 1b study is necessary to evaluate the safety of talimogene laherparepvec in combination with pembrolizumab. In addition, the phase 1b part of the study will evaluate potential blood and [redacted] that associate with response or resistance to talimogene laherparepvec in combination with pembrolizumab. During phase 1b, talimogene laherparepvec will be started 5 weeks preceding pembrolizumab administration and continuing during pembrolizumab administration. This dosing schedule will allow for correlative [redacted] studies to be performed before and after talimogene laherparepvec is combined with pembrolizumab.

An analysis of the phase 1b portion of the study was recently completed (Ribas et al, 2017). Twenty one patients with advanced melanoma were treated with talimogene laherparepvec followed by pembrolizumab. Median follow-up was 18.6 (17.7 to 20.8) months. Therapy was generally well tolerated. No dose-limiting toxicities occurred. The most frequent adverse events were fatigue (62%), fever (43%), chills (48%), and rash (33%). One event of grade 1 cytokine-release syndrome was described as possibly related to the combination. The other serious adverse events were attributed solely to pembrolizumab and included grade 3 autoimmune hepatitis, grade 3 aseptic meningitis and grade 4 pneumonitis (one patient each). The confirmed objective response rate (ORR) was 62% with a complete response (CR) rate of 33% per immune-related response criteria. Responses occurred across all substages of melanoma. Median PFS and OS were not reached at the time of last follow-up. Response to the combination therapy did not appear to be associated with baseline CD8+ T cell infiltration or IFN-gamma signature. Patients who responded to the combination therapy had increased CD8+ T cells, elevated PD-L1 protein expression as well as IFN-gamma gene expression on several cell subsets in the tumors after

talimogene laherparepvec treatment. These findings suggest that talimogene laherparepvec may improve the efficacy of pembrolizumab by changing the tumor microenvironment.

In both phases of the study, pembrolizumab will be administered at a fixed dose of 200 mg either every 2 weeks in phase 1 or every 3 weeks in phase 3. A 2 mg/kg Q3W dose is approved for metastatic melanoma in some countries.

The dosing schedule will be changed from Q2W in phase 1 to Q3W in phase 3 to align with the FDA-approved schedule for pembrolizumab and in consideration of the data. Talimogene laherparepvec will be Q2W starting with the second dose but will switch to Q3W at week 9. The Q2W schedule for talimogene laherparepvec between weeks 3 and 9 will allow for more optimal delivery of talimogene laherparepvec during the period when it is likely that most subjects will have lesions to inject but switch to Q3W at week 9 in order to allow for synchronization of talimogene laherparepvec and pembrolizumab schedules to minimize treatment visits for the subjects still requiring talimogene laherparepvec treatment. The median number of talimogene laherparepvec doses received during phase 1b of the 20110264 study in combination with ipilimumab was six (Puzanov et al, 2014). Although a Q3W schedule for talimogene laherparepvec have not been compared directly against a Q2W schedule in melanoma, clinical activity has been observed in early phase head and neck and pancreatic cancer studies using a Q3W schedule (Chang et al, 2012; Harrington et al, 2010).

2.5 Clinical Hypotheses

Phase 1b:

Talimogene laherparepvec in combination with pembrolizumab will be safe and well tolerated in subjects with previously untreated, unresectable, stage IIIB to IVM1c melanoma.

Phase 3:

Two clinical hypotheses will be evaluated independently in the phase 3. The first clinical hypothesis is that talimogene laherparepvec with pembrolizumab compared to placebo with pembrolizumab will improve PFS as evaluated by a blinded independent central review using modified RECIST 1.1. The second clinical hypothesis is that talimogene laherparepvec with pembrolizumab compared to placebo with pembrolizumab will improve OS.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a phase 1b/3, multicenter, clinical trial. The study will be conducted in 2 parts (phase 1b and phase 3) as described below.

3.1.1 Phase 1b Study Design

Phase 1b is an open-label, multicenter, single-arm study. Talimogene laherparepvec will be administered in combination with pembrolizumab to approximately 20 subjects with previously untreated, unresectable, stage IIIB to IVM1c melanoma to evaluate the safety of talimogene laherparepvec in combination with pembrolizumab. In addition, phase 1b will evaluate potential blood and [redacted] that associate with response or resistance to talimogene laherparepvec in combination with pembrolizumab.

Subjects enrolled in phase 1b will receive talimogene laherparepvec 5 weeks before the initiation of pembrolizumab treatment to evaluate changes in the blood and [redacted] in individuals who receive talimogene laherparepvec monotherapy prior to the addition of pembrolizumab. The start of talimogene laherparepvec will be defined as week -5. The start of pembrolizumab will be defined as week 0. When talimogene laherparepvec and pembrolizumab are administered on the same day, talimogene laherparepvec should be administered first, if possible.

Talimogene laherparepvec will be administered as an intralesional injection up to 4 mL of 10^6 PFU/mL at day 1 of week -5 followed by up to 4 mL of 10^8 PFU/mL at day 1 of week -2 (ie, 21 days later [+3 days]), at day 1 of week 0 (± 3 days), and every 2 weeks (± 3 days) thereafter until disappearance of injectable lesions, CR, confirmed PD per modified immune-related Response Criteria (irRC; Wolchok et al, 2009; Appendix D), intolerance of study treatment, 24 months from the date of the first dose of pembrolizumab, or end of study, whichever occurs first. 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. Therefore, talimogene laherparepvec dosing should continue provided that the subject has no evidence of confirmed PD per modified irRC (Appendix D) and is able to tolerate the treatment.

Pembrolizumab will be administered at a dose of 200 mg, as an intravenous infusion over approximately 30 minutes every 2 weeks (± 3 days) starting at day 1 week 0 (ie, at the time of the third dose of talimogene laherparepvec). Pembrolizumab dosing will continue until confirmed PD per modified irRC, intolerance to treatment, 24 months from the date of the first dose of pembrolizumab, or end of study, whichever occurs first.

For subjects who have attained a confirmed CR, discontinuation of treatment may be considered if the subjects have been treated for at least 24 weeks with pembrolizumab and had at least 2 treatments with pembrolizumab beyond the date when the initial CR was declared.

3.1.1.1 Rules for DLT Evaluation in Phase 1b

A Dose Level Review Team (DLRT) consisting of the Amgen study team, including at least one clinician, safety representative, and biostatistician, at least one representative of the Merck study team, and at least one investigator participating in the study who has recruited subjects into the phase 1b part of the study, was to review the safety data to evaluate possible drug effects and DLT. This team was to recommend either to enroll more subjects for DLT evaluation in phase 1b, to prematurely stop enrollment into phase 1b, or to declare that the combination is tolerable and whether to open phase 3.

The DLT evaluation period is 6 weeks from the initial administration of pembrolizumab. To be evaluable for a DLT, subjects must have had the opportunity to be on treatment for at least 6 weeks from the initial dosing of pembrolizumab and have received at least 2 doses of talimogene laherparepvec and 2 doses of pembrolizumab in combination (ie, on the same day) or otherwise experienced a DLT within 6 weeks after starting the combination therapy. Subjects could be replaced if they were not evaluable for DLT (eg, a subject did not receive study treatment, permanently discontinued talimogene laherparepvec prior to receiving the first dose of pembrolizumab for any reason, or ended the study treatment before completion of DLT evaluation period for a reason other than experiencing a DLT).

The DLRT was to initially meet when 6 subjects are evaluable for DLT. The DLRT was to declare the combination of talimogene laherparepvec and pembrolizumab tolerable if the incidence of DLT is < 33% during the DLT evaluation period subject to the following rules:

- If ≤ 1 subject among the initial 6 evaluable subjects in phase 1b experienced a DLT during the DLT evaluation period, then the combination of talimogene laherparepvec and pembrolizumab would be declared as safe and enrollment in phase 3 would open.
- If 2 subjects among the initial 6 evaluable subjects in phase 1b experienced a DLT during the DLT evaluation period, an additional 3 evaluable subjects would be enrolled in phase 1b.

- If ≤ 2 subjects among the expanded cohort of 9 evaluable subjects in phase 1b experienced a DLT during the DLT evaluation period, then the combination of talimogene laherparepvec and pembrolizumab would be declared as safe and enrollment in phase 3 would open.
- If ≥ 3 subjects among the initial 6 evaluable subjects or among the expanded cohort of 9 evaluable subjects in the phase 1b experienced a DLT during the DLT evaluation period, then the combination of talimogene laherparepvec and pembrolizumab would be declared not safe, the enrollment in phase 1b would end, and phase 3 would not be opened for enrollment.

The DLT evaluation would be based on the initial 6 to 9 subjects meeting the DLT evaluation criteria as outlined above. However, the enrollment would not be halted while the DLT evaluation was still ongoing. Additional subjects, up to a total of approximately 20, would be enrolled in the phase 1b portion of the trial to address the secondary objective exploring the relationship between [redacted] and response to treatment. The DLRT would review additional safety data from subjects enrolled in phase 1b beyond the 6 to 9 DLT evaluable subjects during the DLT review meeting or request an ad hoc review if deemed necessary to further assess the overall safety profile of talimogene laherparepvec in combination with pembrolizumab and would decide whether DLT evaluation of these subjects beyond the first 6 to 9 should be recommended prior to initiating phase 3.

A DLRT meeting was conducted on 19 May 2015 to review safety data after 6 subjects had been treated for at least 6 weeks past the first dose of combination therapy. There were no DLTs in the first 6 subjects. Following review of the cumulative safety data for all subjects enrolled into the phase 1b portion of the study, the DLRT voting attendees, including Amgen and Merck study team members and 4 investigators on the study, unanimously agreed that the reviewed data did not present any safety concerns and that the study can proceed to opening the next phase (data on file).

3.1.1.2 Definition of DLT in Phase 1b

All toxicities will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (Appendix A).

The occurrence of any of the following toxicities during DLT evaluation period (ie, 6-week period from the initial administration of pembrolizumab) will be considered a DLT, if judged by the investigator to be related to the administration of talimogene laherparepvec and/or pembrolizumab:

- Grade 4 non-hematologic toxicity
- Grade 3 or higher pneumonitis

- 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:
  - medical intervention is required, or
  - the abnormality leads to hospitalization, or
  - the abnormality persists for > 1 week
- Febrile neutropenia grade 3 or grade 4:
  - Grade 3 is defined as absolute neutrophil count (ANC) < 1.0 x 10^9/L with a single temperature of > 38.3ºC (101 ºF) or sustained temperature of ≥ 38ºC (100.4ºF) for more than 1 hour
  - Grade 4 is defined as ANC < 1.0 x 10^9/L with a single temperature of > 38.3 ºC (101ºF) or sustained temperature of ≥ 38ºC (100.4ºF) for more than 1 hour, with life-threatening consequences and urgent intervention indicated
- Thrombocytopenia < 25 x 10^9/L if associated with:
  - a bleeding event which does not result in hemodynamic instability but requires an elective platelet infusion, or
  - a life-threatening bleeding event which results in urgent intervention and admission to intensive care unit
- Grade 5 toxicity (ie, death)
- Any other intolerable toxicity leading to permanent discontinuation of talimogene laherparepvec or pembrolizumab

If a subject experiences a DLT during the DLT evaluation period, study treatments will be discontinued for that subject.

3.1.2 Phase 3 Study Design

The phase 3 study is a double-blind, placebo-controlled, multicenter, randomized trial to evaluate the efficacy, as assessed by PFS and OS of talimogene laherparepvec with pembrolizumab versus placebo with pembrolizumab in subjects with unresectable, stage IIIB to IVM1c melanoma. Approximately 660 subjects will be randomized 1:1 to receive the following:

- Arm 1: talimogene laherparepvec plus pembrolizumab
- Arm 2: placebo plus pembrolizumab

Randomization will be stratified by stage of disease: less advanced stages (IIIB, IIIC, and IVM1a) versus more advanced stages (IVM1b and IVM1c) and by prior serine/threonine protein kinase B-Raf BRAF inhibitor therapy: no prior BRAF inhibitor versus prior BRAF inhibitor with or without MEK inhibitor.

Talimogene laherparepvec/placebo and pembrolizumab treatment will be initiated simultaneously. When talimogene laherparepvec/placebo and pembrolizumab are administered on the same day, talimogene laherparepvec/placebo should be administered first, if possible.

Talimogene laherparepvec/placebo will be administered as an intralesional injection up to 4 mL of 10^6 PFU/mL at day 1 of week 0 followed by up to 4 mL of 10^8 PFU/mL at day 1 of week 3 (ie, 21 days later [+3 days]), and every 2 weeks (± 3 days) until the fifth injection of talimogene laherparepvec/placebo (week 9) and then be dosed synchronously with pembrolizumab thereafter every 3 weeks (± 3 days). Talimogene laherparepvec/placebo should be administered until disappearance of injectable lesions, iCR, documented confirmed progressive disease (iPD) per modified irRC-RECIST (Appendix F), intolerance of study treatment, 24 months from the date of the first dose of talimogene laherparepvec/placebo, or end of study, whichever occurs first. 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. Therefore, dosing should continue provided that the subject has no evidence of confirmed iPD per modified irRC-RECIST (Appendix F) and is able to tolerate the treatment.

Pembrolizumab will be administered at a dose of 200 mg, as an intravenous infusion over approximately 30 minutes on day 1 of week 0, day 1 of week 3 (ie, 21 days later [+3 days]), and every 3 weeks (± 3 days) thereafter until confirmed iPD per modified irRC-RECIST (Appendix F), intolerance to treatment, 24 months from the date of the first dose of pembrolizumab, or end of study, whichever occurs first. For subjects who have attained a confirmed iCR, discontinuation of treatment may be considered if the subjects have been treated for at least 24 weeks with pembrolizumab and had at least 2 treatments with pembrolizumab beyond the date when the initial CR was declared.

The first two interim analyses of safety are planned to evaluate the safety of talimogene laherparepvec in combination with pembrolizumab in the target population for phase 3. Planned safety monitoring will occur when approximately 20 and 100 total subjects, respectively, have had the opportunity to be on treatment for at least 6 weeks from the initial dosing of study treatment in phase 3 and have received at least 1 dose of study treatment. Safety monitoring by the Data Monitoring Committee (DMC) will occur approximately every 6 months after the DMC meeting to review the futility analysis for

iORR and iDCR until the primary analysis of OS. Enrollment will not be halted while the interim analysis of safety is ongoing.

Additional interim safety analyses may be performed if warranted based on results from the planned safety and/or interim analyses or if requested by the clinical study team or the DMC. The futility analysis based on iORR and iDCR using modified irRC-RECIST per blinded independent central review is planned to include the first 160 subjects (80 per arm) that have been enrolled and have had an opportunity to be followed for the tumor assessment scheduled at week 24. This futility analysis will be based on Bayesian methods. The talimogene laherparepvec plus pembrolizumab arm is considered to be futile if the posterior probability that at least 6% absolute increase for iORR (at least 10% for iDCR) from the pembrolizumab is < 0.65 (< 0.75 for iDCR). A DMC will be responsible to review interim safety and non-binding futility analyses for iORR and iDCR. The DMC is also responsible to review the results from the primary analysis of PFS by blinded independent central review using modified RECIST 1.1 and all interim OS analyses performed by an external independent biostatistics group. At the time of PFS primary analysis, an interim OS efficacy analysis will be performed by the external biostatistics group and reviewed by the DMC. **The** second interim OS analysis is planned after 282 events have occurred. If OS is not declared statistically significant at the second interim analysis, a non-binding futility analysis will be performed. However, if 282 OS events are observed prior to the event goal for the primary PFS, then the first OS interim will be the event-driven (ie, 282 events) and a PFS interim will be conducted with all PFS events at the time of the 282 OS events interim analysis. In this case, the second OS interim analysis will be performed at the PFS primary analysis with all OS events. **The third interim OS analysis for efficacy is planned after 315 events have occurred.** Refer to Section 10.4.1.4 for additional information.

3.1.3 Tumor Response Assessment

Immunotherapy agents such as talimogene laherparepvec and pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such approaches may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest as a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Therefore, irRC and modified irRC-RECIST will be used in the phase 1b and phase 3, respectively, to account for the unique tumor response characteristics seen with talimogene laherparepvec and pembrolizumab. The irRC, which uses

bidimensional measurements, was found to be highly concordant to a version of irRC using unidimensional measurements (Nishino et al, 2013). Moreover, the concordance between irRC-RECIST 1.0 and 1.1 was also high (Nishino et al, 2014).

3.1.3.1 Phase 1b Tumor Response Assessment

irRC (Wolchok et al, 2009) will be used for the determination of the ORR endpoints in the phase 1b part of the study. Clinical measurements of cutaneous, subcutaneous, and palpable nodal tumor lesions by calipers, photographic imaging of up to 5 (maximum 5 per organ) visible (ie, visible protrusion from skin surface) cutaneous and subcutaneous tumor lesions, and radiographic imaging (computed tomography [CT] scan, positron emission tomography [PET/CT] scan, magnetic resonance imaging, [MRI], or ultrasound [US], if applicable) of all other disease, will be performed according to the schedule of assessment and procedures for phase 1b (refer to Table 5, Section 7.1 and Section 7.2). Note: When a lesion can be accurately evaluated by both radiographic imaging and clinical examination or photographs, radiographic imaging evaluations should be undertaken.

irRC will also be used by the investigator during the phase 1b to determine eligibility and to make treatment decisions.

Up to 5 measurable cutaneous lesions and 10 measurable visceral lesions (maximum 5 per organ) will be selected as index lesions at baseline and will be followed and measured at each subsequent tumor assessment visit. In addition, up to 5 new measurable cutaneous lesions and 10 new measurable visceral lesions (maximum 5 per organ) will be followed, measured, and added to the tumor burden calculations for each subject. If tumor assessments (clinical, photographic, radiographic) show initial response (CR or PR), tumor assessments must be repeated ≥ 4 weeks later in order to confirm the response by the investigator. If a tumor assessment (clinical, photographic, radiographic) after the first dose of pembrolizumab shows initial PD, tumor assessments must be repeated ≥ 4 weeks later in order to confirm PD by the investigator. Subjects will have the option of continuing assigned study treatment while awaiting confirmation of PD. If repeat clinical, photographic, and radiographic assessments show a reduction in the tumor burden compared to the initial assessments demonstrating PD, treatment may be continued. If repeat clinical, photographic, and radiographic assessments confirm PD, subjects will be discontinued from study treatment. In determining whether or not the tumor burden has increased or decreased, investigators should consider all index lesions and new measurable lesions as well as non-index lesions and new

non-measurable lesions. Additional information for tumor response assessments is provided in Appendix D.

In subjects who have initial evidence of PD, it is at the discretion of the investigator to continue a subject on study treatment until repeat imaging is obtained a minimum of 4 weeks later. 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 while waiting for confirmation of PD 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 (eg, cord compression) requiring urgent alternative medical intervention

When feasible, subjects should not be discontinued until PD is confirmed. Subjects who are reported by the investigator as being clinically unstable and not meeting the above criteria for clinical stability are not required to have repeated clinical, photographic, and radiographic assessments for confirmation of PD.

3.1.3.2 Phase 3 Tumor Response Assessment

RECIST 1.1 (Eisenhauer et al, 2009), which includes the following modifications will be used by a blinded independent central review for determination of primary endpoint and some of the secondary tumor response-related endpoints in the phase 3 part of the study (summarized in Appendix G with additional details provided in the independent central review charter):

- Increased total target lesions to a maximum of 10 (up to a maximum of 5 per organ).
- Lesions not measurable on CT or MRI will be considered as non-target only.

A modified version of the irRC-RECIST defined by (Nishino et al, 2014) (Appendix F), will be employed in phase 3 to account for unique tumor response characteristics observed with immunotherapies and enable treatment beyond progression and to simplify the irRC to unidimensional measurements. The modified irRC-RECIST criteria will be used by the investigator during the phase 3 to determine eligibility, make treatment decisions and evaluation of some response-related secondary endpoints based on the investigator review of the clinical photographic and radiographic data.

Photographic imaging of visible (ie, visible protrusion from skin surface) cutaneous and subcutaneous tumor lesions, and radiographic imaging (CT scan, PET/CT scan, or MRI) of all other disease, must be performed during the phase 3 part of the study according to the schedule of assessments and procedures (refer to Table 6, Sections 7.1 and 7.2) and submitted to a blinded independent imaging vendor for evaluation of primary and some of the secondary response-related endpoints by the blinded independent central review. Note: When a lesion can be accurately evaluated by both radiographic imaging and clinical examination or photographs, radiographic imaging evaluations must be undertaken. When a lesion/lesions cannot be evaluated by radiographic imaging, but can be accurately evaluated by both clinical examinations and photographs, photographs must be undertaken. Radiographic images and/or photography (if applicable), should be submitted to the imaging vendor. Additional information will be included in the Site Imaging Manual.

irRC-RECIST is a modification of the RECIST 1.1 criteria that includes the revised guidelines for definition of measurable lesion, number of target lesions, measurement of lymph nodes, and cutoff values of percent changes in tumor burden for PR and PD as described in RECIST 1.1 in addition to the following (See Appendix F):

- Lesions not measurable on CT or MRI will be considered as non-target only.
- Up to 10 (maximum 5 per organ) unidimensional measurable lesions (≥ 10 mm longest diameter for non-nodal lesions and ≥ 15 mm of short axis for lymph nodes) will be selected as target lesions at baseline and will be followed and measured at each subsequent tumor assessment visit. All other lesions, including measurable lesions not selected as target lesions and truly non-measurable lesions, will be followed as non-target lesions.
- At each subsequent tumor assessment, the sum of the diameter of the baseline target lesions and the sum of the diameter of new measurable lesions (up to 10 new measurable lesions [maximum 5 per organ] per time point) are added together to provide the total tumor burden. New nodal lesions must be ≥ 15 mm in short axis to be measurable.
- At each subsequent tumor assessment follow-up the cutoff values defined in RECIST 1.1 are used to determine response. iPR requires a ≥ 30% reduction in tumor burden compared to baseline while iPD requires ≥ 20% increase in tumor burden for iPD compared to the nadir. iCR requires disappearance of all non-nodal lesions, while all nodal lesions must achieve a short axis < 10 mm.
- If tumor assessments (clinical, photographic, and/or radiographic) by investigator show initial iCR or iPR, tumor assessments (clinical, photographic, and/or radiographic) must be repeated ≥ 4 weeks (28 days) later in order to confirm iCR or iPR by the investigator.

- If tumor assessments (clinical, photographic, and/or radiographic) by investigator show initial iPD, tumor assessments (clinical, photographic, and/or radiographic), must be repeated ≥ 4 weeks later in order to confirm iPD by the investigator unless the subject is clinically unstable (Section 3.1.3.1) as indicated by the investigator, in which case confirmation is not necessary for initial iPD. At the discretion of the investigator, subjects with PD may continue on treatment as described in Section 3.1.3.3.
- A ≥ 20% increase in total tumor burden (ie, the sum of the diameter of target lesions plus up to 10 [maximum 5 per organ] new measurable lesions) compared to the nadir at two consecutive time points at least 4 weeks (28 days) apart will be considered confirmed iPD (with the date of progression considered to be the time of the initial evaluation showing iPD).

  Note: Unequivocal progression of non-measureable lesions only does not result in overall iPD.

Refer to Appendix F for additional instructions regarding tumor response assessments using modified irRC-RECIST guidelines.

3.1.3.3 Subject Management After Radiographic Progression During Phase 3

- If, following initial iPD, repeat clinical, photographic, and/or radiographic assessments show stable disease (SD), iPR, or iCR treatment may be continued as per treatment schedule and the prior evaluation will not be considered as a progression event.
- If, following initial iPD, repeat clinical, photographic, and/or radiographic assessments confirm iPD without reduction in tumor burden compared to previous time-point, subjects will be discontinued from study treatment unless granted exception as stated in the note section below.
- A ≥ 20% increase in total tumor burden (ie, the sum of the diameter of target lesions identified at baseline and up to 10 [maximum 5 per organ] new measurable lesions per time point) compared to the nadir at two consecutive time points at least 4 weeks (28 days) apart will be considered confirmed iPD. Additional information for tumor response assessments is provided in Appendix F.

The decision to continue study treatment after the first evidence of iPD is at the investigator's discretion based on the clinical status of the subject as described in Table 1.

Table 1. Imaging and Treatment After First Evidence of iPD

	Clinically Stable		Clinically Unstable	
	Assessments	Treatment	Assessments	Treatment
1st clinical, photographic, and/or radiographic evidence of iPD	Repeat clinical, photographic, and/or radiographic assessments ≥ 4 week at site to confirm iPD	May continue study treatment at the investigator's discretion while awaiting confirmatory assessments by the site	Repeat clinical, photographic, and/or radiographic assessments ≥ 4 week at site to confirm iPD per investigator's discretion only	Discontinue study treatment
Repeat clinical, photographic, and/or radiographic assessments confirm iPD (no reduction in tumor burden from prior assessments)	No additional clinical photographic, and/or radiographic assessments required	Discontinue study treatment unless granted exception as stated in the note section below.	No additional clinical photographic, and/or radiographic assessments required	Discontinue study treatment
Repeat clinical, photographic, and/or radiographic assessments do not confirm iPD (reduction in tumor burden from prior assessments)	May continue regularly scheduled clinical photographic, and/or radiographic assessments after medical monitor consultation	May continue study treatment after consultation with the sponsor medical monitor	May continue regularly scheduled clinical photographic, and/or radiographic assessments after medical monitor consultation	May restart study treatment if condition has improved and/or clinically stable per investigator's and medical monitor's discretion
Repeat clinical, photographic, and/or radiographic assessments show iSD, iPR, or iCR	Continue regularly scheduled clinical photographic, and/or radiographic assessments	Continue study treatment at the investigator's discretion	Continue regularly scheduled clinical photographic, and/or radiographic assessments	May restart study treatment if condition has improved and/or clinically stable per investigator's discretion

iCR = complete response; iPD = progressive disease; iPR = partial response; iSD = stable disease

Confirmatory clinical, photographic, and/or radiographic assessments may be performed as early as 4 weeks (28 days) later; alternatively, the assessments at the next schedule tumor response assessment visit (every 12 weeks +7) may be used for confirmation of iPD. The 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 while waiting for confirmation of iPD if they are clinically stable as defined by all of the following criteria:

- Absence of signs and symptoms (including worsening of laboratory values) indicating iPD
- 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 (eg, cord compression) requiring urgent alternative medical intervention

Subjects exhibiting intolerable toxicity from the study treatment may not continue to receive study treatment.

Note: If a subject with confirmed iPD (ie, two consecutive tumor assessments at least 4 weeks [28 days] apart demonstrating iPD) is clinically stable or clinically improved, and there is no further increase in tumor burden at the confirmatory assessments (assessed by the investigator and site radiologist, if applicable), an exception may be considered to continue treatment upon consultation with the sponsor medical monitor.

3.1.4 Follow-up

3.1.4.1 Safety Follow-up

Subjects enrolled in phase 1b and phase 3 will be followed for safety approximately 30 (+7) days after the last dose of study treatment. If an end of treatment decision occurs > 30 (+7) days after the last treatment date, then the Safety follow-up should be performed as soon as possible (eg, within a week of the end of treatment decision). Applicable safety follow-up procedures should occur even if the subject has initiated new anticancer therapy. Serious adverse events observed by the investigators or reported by the subjects that occur within 90 (+7) days after the cessation of all study treatment or 30 (+7) days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, will be reported, followed, and recorded as described in Section 9.2.1.2.

3.1.4.2 Long-term Follow-up

Subjects enrolled in phase 1b and phase 3 will be followed for survival, subsequent anticancer therapies, and injected investigational product-related adverse events for every 12 weeks (± 28 days) for approximately 60 months after the last subject is randomized in phase 3.

For subjects who discontinue study treatment without documented PD, every effort should be made to continue monitoring tumor response status by clinical, photographic,

and radiographic assessments, and to complete PRO questionnaires every 12 weeks (+1 week) until documented confirmed PD per modified irRC in phase 1b (Appendix D) or iPD per modified irRC-RECIST in phase 3 (Appendix F), start of new anticancer treatment, death, or end of study, whichever occurs first. For subjects with PD (see footnote cc of Table 6), QLQ-C30 will no longer be collected, and EQ-5D-3L will be collected through the long-term follow-up. Subjects who have reached a confirmed CR may increase their interval of radiographic assessments up to 6 months (26 weeks) after the first 2 years beyond confirmed CR and up to 12 months (52 weeks) after the first 5 years beyond confirmed CR as long as CR is maintained. For subjects with PD, EQ-5D-3L may be collected via telephone.

Subjects who have received talimogene laherparepvec (all subjects in phase 1b and those who received talimogene laherparepvec in phase 3) and completed the protocol-specified follow-up period for a reason other than death or withdrawal of full consent will be eligible to continue follow-up in a separate ongoing registry protocol which is in place for the long-term survival follow-up of subjects treated with talimogene laherparepvec in clinical trials. The registry protocol, including for phase 1b subjects, will not apply until the end of the study or 5 years after the last subjects enrolled in phase 3, whichever comes first. The registry protocol will also monitor for late and long-term adverse events thought to be potentially related to talimogene laherparepvec.

The overall study design of phase 1b and phase 3 is described by study schemas at the end of the protocol synopsis section.

The study endpoints are defined in Section 10.1.1.

3.2 Number of Sites

The study will be conducted at approximately 175 sites in Australia, Europe, North America, and other regions. Additional sites and countries may be added.

Sites that do not enroll subjects within approximately 4 months of site initiation may be closed.

3.3 Number of Subjects

Participants in this clinical investigation shall be referred to as “subjects”.

Approximately 680 subjects will be enrolled in this study: approximately 20 subjects will be enrolled in phase 1b and approximately 660 subjects will be enrolled in phase 3.

Refer to Section 10.2 for sample size considerations.

3.4 Replacement of Subjects

Subjects enrolled in phase 1b may be replaced if they are not evaluable for DLT (eg, did not receive study treatment, permanently discontinued talimogene laherparepvec prior to receiving the first dose of pembrolizumab for any reason, or ended the study treatment before completion of DLT evaluation period for a reason other than experiencing a DLT).

Subjects enrolled in phase 3 who are withdrawn or removed from treatment or from the study will not be replaced.

3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

The duration for the study from the initiation of phase 1b is approximately 8 years (96 months). The duration of screening for each subject will be approximately 28 days. The subject accrual period for phase 1b is planned for approximately 6 months from the initiation of phase 1b. The subject accrual period for phase 3 is planned for approximately 20 months (depending on average per month enrollment rates) from the initiation of phase 3. The duration of treatment will vary for each subject. Subjects enrolled in phase 1b and phase 3 parts of the study will be treated for up to approximately 24 months. Subjects will be followed for safety approximately 30 (+7) days after the last dose of study treatment and for serious adverse event reporting approximately 90 (+7) days after the cessation of all study treatment or 30 (+7) days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. If an end of treatment decision occurs > 30 (+7) days after the last treatment date, then the Safety follow-up should be performed as soon as possible (eg, within a week of the end of treatment decision). Subjects will be followed for survival for approximately 60 months after the last subject is randomized in phase 3.

The end of study for each subject is defined as the date the subject withdraws full consent from the study, completes the safety follow-up visit or the long-term survival follow-up, whichever is later, or death.

3.5.2 End of Study

Primary Completion: The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s).

The primary completion date is the date when data for the primary endpoint**(s)** are last collected for the purpose of conducting the primary analysis.

If the study concludes prior to the primary completion date originally planned in the protocol (ie, early termination of the study), then the primary completion will be the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit).

End of Study: The end of study date is defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable.

4. SUBJECT ELIGIBILITY

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (eg, date of screening).

Before any study-specific activities/procedure, the appropriate written informed consent must be obtained (see Section 11.1).

4.1 Inclusion and Exclusion Criteria

4.1.1 Inclusion Criteria

4.1.1.1 Inclusion Criteria for Phase 1b and Phase 3

101 Subject has provided informed consent prior to initiation of any study-specific activities/procedures

102 Male or female age ≥ 18 years at the time of informed consent

103 Histologically confirmed diagnosis of melanoma

104 Disease stage **defined as one of the following (per the seventh edition of the American Joint Committee on Cancer [AJCC] Cancer Staging Manual)**: Subject with unresectable stage IIIB, IIIC, IVM1a, IVM1b, or IVM1c melanoma

107 Candidate for intralesional therapy defined as either one of the following:

- at least 1 injectable cutaneous, subcutaneous, or nodal melanoma lesion ≥ 10 mm in longest diameter
- multiple injectable melanoma lesions that in aggregate have a longest diameter of ≥ 10 mm injectable disease

108 ECOG performance status of 0 or 1

109 Adequate organ function determined within 14 days prior to enrollment, defined as follows:

- Hematological
  - ANC ≥ 1.5 x 10^9/L
  - platelet count ≥ 100 x 10^9/L
  - hemoglobin ≥ 9 g/dL (without need for hematopoietic growth factor or transfusion support)

- Renal
  - serum creatinine ≤ 1.5 x upper limit of normal (ULN), OR 24-hour creatinine clearance ≥ 60 mL/min for subject with creatinine levels > 1.5 x ULN. (Note: Creatinine clearance need not be determined if the baseline serum creatinine is within normal limits. Creatinine clearance should be calculated per institutional standard).
- Hepatic
  - serum bilirubin ≤ 1.5 x ULN OR direct bilirubin ≤ ULN for a subject with total bilirubin level > 1.5 x ULN
  - aspartate aminotransferase (AST) ≤ 2.5 x ULN OR ≤ 5 x ULN for subject with liver metastases
  - alanine aminotransferase (ALT) ≤ 2.5 x ULN OR ≤ 5 x ULN for subject with liver metastases
- Coagulation
  - international normalization ratio (INR) or prothrombin time (PT) ≤ 1.5 x ULN unless the subject is receiving anticoagulant therapy as long as PT and partial thromboplastin time (PTT)/activated PTT (aPTT) is within therapeutic range of intended use of anticoagulants

110 Female subject of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to enrollment. If the urine pregnancy test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

4.1.1.2 Inclusion Criteria Specific to Phase 1b

105 Prior therapy for melanoma inclusion requirement: Treatment naïve: Must not have received any prior systemic anticancer treatment consisting of chemotherapy, immunotherapy, or targeted therapy given in a non-adjuvant setting for unresectable stage IIIB to IVM1c melanoma
Note: Subjects who received prior adjuvant therapy for melanoma will not be excluded (including, but not limited to radiotherapy, interferon, limb infusion/perfusion, or use of investigational agents in the adjuvant setting). However, if the subject received a course of adjuvant therapy, the subject must have ended therapy at least 3 months prior to enrollment. If adjuvant therapy was not completed due to intolerance, the subject must have ended therapy at least 3 months prior to enrollment. No prior pembrolizumab, other anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, ipilimumab, other CTLA-4 inhibitor, talimogene laherparepvec, tumor vaccine, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways is allowed, even if given in the adjuvant setting.

106 Measurable disease: defined as either one of the following:

- at least 1 visceral or nodal/soft tissue melanoma lesion (including lymph nodes) that can be accurately and serially measured in at least 2 dimensions and for which the longest diameter is ≥ 10 mm as measured by CT scan or MRI

- at least 1 superficial cutaneous or subcutaneous melanoma lesion that can be accurately and serially measured in at least 1 dimension and for which the longest diameter is ≥ 10 mm as measured by calipers

4.1.1.3 Inclusion Criteria Specific to Phase 3

105 $BRAF^{V600}$ wild-type: Subjects with $BRAF^{V600}$ wild-type tumors must not have received any prior systemic anticancer treatment consisting of chemotherapy, immunotherapy, or targeted therapy given in a non-adjuvant setting for unresectable stage IIIB to IVM1c melanoma.

$BRAF^{V600}$ mutation: Subjects with $BRAF^{V600}$ mutated tumors who have received prior BRAF inhibitor therapy either alone or in combination with MEK inhibitor as their only prior line of systemic therapy are eligible for this study. However, the subject must have ended BRAF inhibitor therapy either alone or in combination with MEK inhibitor at least 14 days prior to enrollment and have adequately recovered from any treatment-related adverse events (ie, ≤ Grade 1 or baseline).

Subjects with $BRAF^{V600}$ mutant melanoma or unknown $BRAF^{V600}$ mutation status who have not received a BRAF inhibitor are also eligible for the phase 3 of this study as first-line treatment if they meet the following criteria: lactate dehydrogenase (LDH) < ULN, no clinically significant tumor related symptoms, and absence of rapidly progressing metastatic melanoma.

Note: Subjects (BRAF mutant, wildtype and UNK) who received prior adjuvant therapy for melanoma will not be excluded (including, but not limited to radiotherapy, interferon, limb infusion/perfusion, ipilimumab, or use of investigational agents in the adjuvant setting). However, the subject must have ended therapy at least 28 days prior to enrollment. No prior anti-CD137, ipilimumab or other CTLA-4 inhibitor, talimogene laherparepvec, tumor vaccine, or any other oncolytic viruses or drugs specifically targeting T-cell co-stimulation or checkpoint pathways are allowed in a non-adjuvant setting. No prior pembrolizumab or any other inhibitor of PD-1, PD-L1, or PD-L2 are allowed in any setting.

106 Measurable disease defined as:

- at least 1 visceral or nodal/soft tissue melanoma lesion that can be accurately and serially measured in at least 1 dimension and for which the longest diameter is ≥ 10 mm as measured by CT scan or MRI. Lymph nodes must measure ≥ 15 mm in their short axis to be considered measurable by CT scan or MRI

111 Subject has a tumor sample (archival sample obtained within 3 months prior to day 1 and no systemic therapy given 3 months prior to archival biopsy or newly obtained biopsy) that is submitted for PD-L1 assessment prior to randomization. Subject must submit the tumor sample during screening for PD-L1 expression testing at a central laboratory. Subjects will be eligible to participate regardless of the level of PD-L1 expression. Subjects with an unevaluable archival sample for PD-L1 expression testing and $BRAF^{V600}$ mutation testing may obtain a new biopsy and subjects with an unevaluable newly obtained biopsy may undergo re-biopsy at the discretion of the investigator. If repeat sample is also unevaluable and the subject is otherwise eligible, the investigator may enroll the subject with or without a second re-biopsy. Subjects with an unevaluable newly obtained biopsy may undergo re-biopsy at the discretion of the investigator. If

the subject is ready to be randomized and treated after re-biopsy, randomization and start of treatment may proceed.

4.1.2 Exclusion Criteria – Phase 1b and Phase 3

201 Clinically active cerebral melanoma metastases and/or carcinomatous meningitis. Subjects with up to 3 cerebral metastases may be enrolled, provided that all lesions have been adequately treated with stereotactic radiation therapy, craniotomy, or gamma knife therapy, with no evidence of progression and not requiring steroids for at least 2 months prior to enrollment. Carcinomatous meningitis is excluded regardless of clinical stability.

202 Primary uveal or mucosal melanoma

203 History or evidence of melanoma associated with immunodeficiency states (eg, hereditary immune deficiency, organ transplant, or leukemia)

204 History of other malignancy within the past 3 years with the following exceptions:

- malignancy treated with curative intent and with no known active disease present and has not received chemotherapy for ≤ 3 years before enrollment and felt to be at low risk for recurrence by the treating physician
- adequately treated non-melanoma skin cancer without evidence of disease at the time of enrollment
- adequately treated cervical carcinoma in situ without evidence of disease at the time of enrollment
- adequately treated breast ductal carcinoma in situ without evidence of disease at the time of enrollment
- prostatic intraepithelial neoplasia without evidence of prostate cancer at the time of enrollment
- adequately treated superficial or in-situ carcinoma of the bladder without evidence of disease at the time of enrollment

205 Prior therapy with talimogene laherparepvec or any other oncolytic viruses

206 Prior therapy with tumor vaccine (unless administered in the adjuvant setting)

207 Prior therapy with pembrolizumab or any other inhibitor of PD-1, PD-L1 or PD-L2. Prior therapy in a non-adjuvant setting with anti-CD137, or anti-CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).

208 Prior mAb therapy within 28 days prior to enrollment or who has not recovered (ie, ≤ grade 1 or at baseline) from adverse events due to agents administered more than 28 days earlier

209 Currently receiving treatment in another investigational device or drug study, or less than 28 days since ending treatment on another investigational device or drug study

210 Expected to require other cancer therapy while on study with the exception of local radiation treatment to the site of bone and other metastasis for palliative pain management

211 Other investigational procedures while participating in this study.

212 History or evidence of symptomatic autoimmune glomerulonephritis, vasculitis, or other symptomatic autoimmune disease, or active autoimmune disease or syndrome that has required systemic treatment in the past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs) except vitiligo or resolved childhood asthma/atopy. Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

213 Evidence of clinically significant immunosuppression such as the following:

- diagnosis of immunodeficiency
- concurrent opportunistic infection
- receiving systemic immunosuppressive therapy (> 2 weeks) or within 7 days prior to the first dose of study treatment, including oral steroid doses > 10 mg/day of prednisone or equivalent except for management of adverse events and central nervous system (CNS) metastases during the course of the study. Subjects that require intermittent use of bronchodilators or local steroid injection will not be excluded from the study.

214 Active herpetic skin lesions or prior complications of herpetic infection (eg, herpetic keratitis or encephalitis)

215 Require intermittent or chronic treatment with an antiherpetic drug (eg, acyclovir), other than intermittent topical use

216 Known human immunodeficiency virus (HIV) disease

217 Known acute or chronic hepatitis B or hepatitis C infection

218 Received live vaccine within 28 days prior to enrollment

219 Female subject is pregnant or breast-feeding, or planning to become pregnant 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

220 Female subject of childbearing potential who is unwilling to use acceptable method(s) of effective contraception 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. Note: Women not of childbearing potential are defined as:

- 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

- have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;

OR

- has a congenital or acquired condition that prevents childbearing.

Note: Acceptable methods of effective contraception are defined in the informed consent form. Where required by local laws and regulations, additional country-specific contraception requirements may be outlined in a country-specific protocol supplement at the end of the Appendix Section of the protocol.

221 Male subject who is unwilling to use acceptable method of effective contraception during pembrolizumab treatment and through 4 months after the last dose of pembrolizumab. 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). Note: Acceptable methods of effective contraception are defined in the informed consent form. Additional country-specific contraception requirements may be defined in a country-specific protocol supplement at the end of the Appendix Section of protocol as required by local laws and regulations.

222 Subject has known sensitivity to any of the products or components to be administered during dosing

223 Subject likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures to the best of the subject and investigator's knowledge

224 History or evidence of psychiatric, substance abuse, or any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion

225 Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling, or child) who is investigational site or sponsor staff directly involved in the this trial, unless prospective institutional review board (IRB)/independent ethics committee (IEC) approval (by chair or designee) is given allowing exception to this criterion for a specific subject

226 Sexually active subjects and their partners unwilling to use a male or female latex condom to avoid potential viral transmission during sexual contact while on-treatment and within 30 days after treatment with talimogene laherparepvec. For those with latex allergies, polyurethane condoms may be used

227 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 (immunosuppressed individuals, HIV-positive individuals, 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

228 Has undergone prior allogeneic hematopoietic stem cell transplantation within the last 5 years. (Subjects who have had a transplant greater than 5 years ago are eligible as long as there are no symptoms of Graft versus Host Disease.)

229 Has a known history of active Bacillus tuberculosis

230 Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis

5. SUBJECT ENROLLMENT

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written IRB/IEC approval of the protocol, informed consent form, and all other subject information and/or recruitment material, if applicable (see Section 11.2). All subjects must personally sign and date the informed consent form before commencement of study-specific activities/procedures.

Each subject who enters into the screening period for the study (defined as the point when the subject signs the informed consent) receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned by the interactive voice response system (IVRS). The subject identification number will not be the same as the randomization number assigned for subjects participating in phase 3. This subject identification number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

Subjects who are determined not eligible after screening must be screen-failed in the IVRS and the reason for the screen-failure provided. Subjects who do not meet all eligibility criteria may be rescreened once at the discretion of the investigator. If a subject is being rescreened, he or she may need to reconsent to the study to ensure that the IRB/IEC approved main informed consent form is signed within 28 days of enrollment or randomization. Subjects who are determined not eligible after rescreen must be screen-failed in the IVRS and the reason for the screen-failure provided. Subjects only may be enrolled or randomized once into this study.

Upon confirmation of eligibility, the site staff will use the IVRS to enroll or randomize a subject. The investigator is to document this decision and date, in the subject's medical record and in/on the enrollment CRF. For the phase 1b portion, the subjects will be considered enrolled upon being registered as enrolled in the IVRS. For the phase 3 portion subjects will be considered enrolled upon randomization in the IVRS. The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened.

5.1 Randomization During Phase 3

Upon confirmation of eligibility, the site staff will use the IVRS to randomize a subject.

The IVRS will assign a randomization number. Approximately 660 subjects will be stratified according to stage of disease: less advanced stages (IIIB, IIIC, and IVM1a)

versus more advanced stages (IVM1b and IVM1c) and by prior BRAF inhibitor therapy: no prior BRAF inhibitor versus prior BRAF inhibitor with or without MEK inhibitor, and randomized with a 1:1 ratio to receive the following:

- Arm 1: talimogene laherparepvec plus pembrolizumab
- Arm 2: placebo plus pembrolizumab

Following randomization via the IVRS, study treatment must commence within 5 days.

Eligible subjects must be registered as randomized subjects in the IVRS before the administration of protocol-specified therapy.

The randomization date is to be documented in the subject's medical record and on the enrollment CRF.

The subject, site personnel, and Amgen study personnel and designees are blinded to the randomization treatment group assignment unless otherwise specified in this protocol. Refer to Section 10.3 for details on when and how the randomization code may be unblinded.

5.2 Site Personnel Access to Individual Treatment Assignments

Talimogene laherparepvec or placebo may be supplied as open label or blinded product. Where talimogene laherparepvec or placebo is supplied open label, the site pharmacist or designee will need to be unblinded to prepare blinded talimogene laherparepvec/placebo. However, all precaution and efforts, including independent monitoring and tracked records, will be taken to ensure the Sponsor and blinded site personal will remain blinded to the study treatment.

- For talimogene laherparepvec or placebo supplied as open-label investigational medicinal product IVRS will confirm to the unblinded site pharmacist or designee from which lot number(s) vials must be selected for a patient visit. In no circumstances should an unblinded pharmacist reveal the treatment assignment to other site staff.
- For talimogene laherparepvec or placebo supplied as blinded investigational medicinal product IVRS will confirm to the site pharmacist or designee from which box number(s) vials must be selected for a patient visit. All site personnel will be blinded to study treatment.

A subject's treatment assignment should only be unblinded when knowledge of the treatment is essential for the further management of the subject on this study and/or for determining eligible treatment options outside of the trial after the subject discontinues study treatment due to documented disease progression. In the event that a subject's treatment assignment must be unblinded by the investigator using the IVRS unblinding

module, the subject will require review by the medical monitor to determine if they will be allowed to receive any further investigational product. Unblinding at the study site for any other reason will be considered a protocol deviation.

The principal investigator is strongly encouraged to contact the sponsor before unblinding any subject's treatment assignment, but must do so within 1 working day after the event and must document the unblinding in the subject's electronic case report form.

6. TREATMENT PROCEDURES

6.1 Classification of Products

The Amgen investigational product used in this study: talimogene laherparepvec or placebo.

The Non-Amgen investigational product used in this study: pembrolizumab.

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, and administration of talimogene laherparepvec and pembrolizumab.

6.2 Investigational Products

6.2.1 Amgen Investigational Product: Talimogene Laherparepvec or Placebo

Talimogene laherparepvec and placebo will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures. The supply for the 10^6 PFU/mL concentration will be packaged separately from the supply for the 10^8 PFU/mL concentration.

Placebo (talimogene laherparepvec formulation excipients as described in the Talimogene Laherparepvec Investigator's Brochure) will be supplied as sterile frozen liquid is the same presentation, packaging and with blinded labelling as for talimogene laherparepvec.

6.2.1.1 Talimogene Laherparepvec or Placebo Dosage, Administration, and Schedule

Talimogene laherparepvec or placebo must be prepared and administered by a qualified healthcare professional. Subjects should be assessed clinically for adverse events/toxicity prior to each dose using the CTCAE version 4 (Appendix A). Complete blood count with differential and chemistry panels including liver function laboratory tests (ALT, AST, and total bilirubin) and thyroid function tests (triiodothyronine [T3] or free T3 [FT3] per local standard, free thyroxine [FT4], and thyroid stimulating hormone [TSH])

should be obtained according to the Schedule of Assessments (up to 3 days before dosing, see Table 5 and Table 6) and the results should be checked prior to the administration of scheduled dose of study drugs. Dosing will occur only if these test values are acceptable, per Section 6.2.1.2.

Note: Thyroid function tests must be collected, but if there are no symptoms of hypothyroidism or hyperthyroidism, study treatment can be initiated prior to the reporting of the laboratory results.

Talimogene laherparepvec or placebo will be administered by intralesional injection only into injectable cutaneous, subcutaneous, and nodal tumors, with or without image ultrasound guidance. Talimogene laherparepvec or placebo must not be administered into visceral organ metastases.

The first cycle of talimogene laherparepvec or placebo will be 21 (+3) days. Subsequent cycles should be given in phase 1 every 2 weeks (± 3) days and in phase 3 every 2 weeks (± 3) days until week 9 and every 3 weeks (± 3) days thereafter. On day 1 of cycle 1 the first dose of talimogene laherparepvec will be up to 4.0 mL of 10^6 PFU/mL or placebo. The second injection up to 4.0 mL of 10^8 PFU/mL should be administered 21 (+3) days after the initial injection (ie, no sooner than day 22 but should not be delayed more than 3 days after the 21-day time point).

The treatment cycle interval may be increased due to toxicity as described in Section 6.2.1.2. When talimogene laherparepvec or placebo injections and pembrolizumab are administered on the same day, talimogene laherparepvec or placebo should be administered first, if possible.

The maximum volume of talimogene laherparepvec or placebo administered at any dose is 4.0 mL for any individual lesion. The maximum dose in any treatment is 4.0 mL. Investigators are encouraged to use the maximum amount whenever lesions' properties allow. Dose reduction for adverse events is not allowed. However, if in the course of administration of talimogene laherparepvec or placebo 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.

The recommended volume of talimogene laherparepvec or placebo to be injected into the tumor(s) is dependent on the size of the tumor(s) and should be determined according to the injection volume guideline in Table 2.

Table 2. Talimogene Laherparepvec or Placebo 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

For subjects enrolled in phase 1b: At baseline, if there are ≥ 2 lesions, one lesion (ie, the lesion considered lowest priority for injection) amenable for biopsy should be left uninjected at least until it is biopsied at time of initial PR, confirmed disease progression, or week 24 for subjects with stable disease (SD), whichever comes first.

For subjects randomized to phase 3: At baseline, if there are ≥ 2 lesions, one lesion (ie, the lesion considered lowest priority for injection) amenable for biopsy should be left uninjected at least until it is biopsied at week 5 (see Section 7.2.2). Aside from leaving one lesion uninjected, all other reasonably injectable lesions (cutaneous, subcutaneous and nodal disease that can be injected with or without ultrasound guidance) should be injected with the maximum dosing volume available on an individual dosing occasion (Table 2). On each treatment day, prioritization of injections is recommended as follows:

- any tumor that does not correspond to the uninjected lesion reserved for biopsy until week 24 (phase 1b) or week 5 (phase 3)
- any new injectable tumor that has appeared since the last injection
- by tumor size, beginning with the largest tumor
- any previously uninjectable tumor(s) that is now injectable

It is recommended that each lesion should receive the maximum amount possible to inject due to tumor properties at each visit before moving on to the next lesion, using the prioritization model above and the injection volume guideline based on tumor size per Table 2. 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.

For phase 1b and phase 3, subjects will be treated with talimogene laherparepvec until subjects have achieved a CR, all injectable tumors have disappeared, confirmed PD per modified irRC in phase 1b (Appendix D) or iPD per modified irRC-RECIST in phase 3 (Appendix F), intolerance of study treatment, 24 months from the date of the first dose of pembrolizumab, or end of study, whichever occurs first. 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. Therefore, talimogene laherparepvec or placebo dosing should continue provided that the subject has no evidence of confirmed PD per modified irRC in phase 1b (Appendix D) or iPD per modified irRC-RECIST in phase 3 (Appendix F) and is able to tolerate the treatment.The dose, start date, and lot/box number of talimogene laherparepvec/placebo are to be recorded on the electronic CRF as per the recommendation found in the electronic CRF completion guidelines.

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

If talimogene laherparepvec/placebo 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 or placebo are not permitted, other than with respect to a reduction in the volume injected due to a disease response.

If a subject experiences any of the following treatment-related toxicities, talimogene laherparepvec/placebo 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

Subjects who are receiving talimogene laherparepvec or placebo 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 or placebo 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 pembrolizumab or talimogene laherparepvec/placebo related toxicities, talimogene laherparepvec or placebo dosing must be withheld until the corticosteroid dose has decreased to 10 mg or < 10 mg prednisone daily (or equivalent).

All necessary supportive therapies except for those listed in Section 6.8 shall be available to subjects. Talimogene laherparepvec or placebo treatment should be continued based on the potential benefit/risk assessment of the subject.

If talimogene laherparepvec or placebo 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.

If talimogene laherparepvec or placebo 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) for reasons other than treatment-related toxicity, the case must be reviewed by the Amgen medical monitor in conjunction with the investigator to determine if the subject can resume talimogene laherparepvec therapy. Talimogene laherparepvec or placebo doses may be given no less than 8 days apart (eg, day 1 and day 9), if needed, for the purpose of re-aligning dosing schedules for talimogene laherparepvec or placebo injections and pembrolizumab after a dose delay. The 8 day dosing should only be used for re-aligning the talimogene laherparepvec or placebo and pembrolizumab schedule. It should not be utilized to bring doses back to schedule. The allowable protocol dosing windows should be used for this purpose.

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

- Phase 1b subject developed DLT during the DLT evaluation period.
- The subject, for any reason, requires treatment with another anticancer therapeutic agent for treatment of the study disease (other than the exceptions noted in Section 6.8). In this case, discontinuation from the treatment occurs immediately upon introduction of the new agent.
- Confirmed PD occurs as defined per the modified irRC in phase 1b (Appendix D) or iPD per modified irRC-RECIST in phase 3 (Appendix F).
- 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 effective contraception (for those subjects who are able to conceive).
- A female subject breast feeds while on study treatment.
- 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 special warnings and precautions for the use of talimogene laherparepvec please refer to the latest version of the Talimogene Laherparepvec Investigator's Brochure.

6.2.2 Non-Amgen Investigational Product: Pembrolizumab

Non-Amgen investigational product pembrolizumab will also be used in this study.

Pembrolizumab will be manufactured by Merck. Pembrolizumab will be labeled, packaged, and distributed by Amgen (or designee) using Amgen (or designee) clinical study drug distribution procedures. Pembrolizumab is supplied as pembrolizumab 100 mg/4 mL vials (25 mg/mL) solution for intravenous infusion.

Additional details regarding the pembrolizumab product are provided in the IPIM.

6.2.2.1 Pembrolizumab Dosage, Administration, and Schedule

Pembrolizumab must be prepared and administered by a qualified healthcare professional. Subjects should be assessed clinically for adverse events/toxicity prior to each dose using the CTCAE version 4 (Appendix A). Complete blood count with differential and chemistry panels including liver function laboratory tests (ALT, AST, and total bilirubin) and thyroid function tests (triiodothyronine [T3] or FT3 per local standard, free thyroxine [FT4], and thyroid stimulating hormone [TSH]) should be obtained according to the Schedule of Assessments (up to 3 days before dosing, see Table 5 and Table 6) and the results should be checked before each applicable treatment. Dosing will occur only if these test values are acceptable, per Section 6.2.2.2.

Note: Thyroid Function Tests must be collected, but if there are no symptoms of hypothyroidism or hyperthyroidism, study treatment can be initiated prior to the reporting of the laboratory results.

In phase 1b, pembrolizumab at a dose of 200 mg will be administered intravenously every 2 weeks (± 3 days). In phase 3 pembrolizumab at a dose of 200 mg will be administered intravenously every 3 weeks (± 3 days). In phase 3, the second dose of pembrolizumab will be administered 21 (+3) days after the initial dose. The treatment cycle interval may be increased due to toxicity as described in Section 6.2.2.2. When talimogene laherparepvec and pembrolizumab are administered on the same day, talimogene laherparepvec should be administered first, if possible.

For phase 1b and phase 3, pembrolizumab dosing will continue until confirmed PD per the modified irRC in phase 1b (Appendix D) or iPD per modified irRC-RECIST in phase 3 (Appendix F), intolerance to treatment, 24 months from the date of the first dose of pembrolizumab, or end of study, whichever occurs first. For subjects who have attained a confirmed CR, discontinuation of treatment may be considered if the subjects have been treated for at least 24 weeks with pembrolizumab and had at least 2 treatments with pembrolizumab beyond the date when the initial CR was declared.

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 (ie, 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. Details on the preparation and administration are provided in the IPIM.

The dose, start date, and lot number of pembrolizumab are to be recorded on the electronic CRF.

6.2.2.2 Pembrolizumab Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 3 below See Section 6.2.2.3 for supportive care guidelines, including use of corticosteroids.

Table 3. Pembrolizumab-related Adverse Event Management

General instructions:

Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.

For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab 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.

For severe and life-threatening irAEs, intravenous 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 1-2 mg/kg prednisone or equivalent) followed by taper	Monitor participants for signs and symptoms of pneumonitis Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		

Footnotes defined on last page of table

Table 3. Pembrolizumab-related Adverse Event Management

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

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Footnotes defined on last page of table

Table 3. Pembrolizumab-related Adverse Event Management

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
AST/ALT elevation or Increased bilirubin	Grade 2	Withhold	Administer corticosteroids (initial dose of 0.5 - 1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	Administer corticosteroids (initial dose of 1-2 mg/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	Initiate insulin replacement therapy for participants with T1DM Administer anti-hyperglycemic in participants with hyperglycemia	Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated.	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue1		

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Footnotes defined on last page of table

Table 3. Pembrolizumab-related Adverse Event Management

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
Hypothyroidism	Grade 2-4	Continue	Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	Monitor for signs and symptoms of thyroid disorders
Nephritis and Renal dysfunction	Grade 2	Withhold	Administer corticosteroids (prednisone 1 – 2 mg/kg or equivalent) followed by taper.	Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		

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Footnotes defined on next page of table

Table 3. Pembrolizumab-related Adverse Event Management

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
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	Based on type and severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

[1] Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

NOTE:

For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when adverse event resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

For myocarditis, in certain circumstances, pembrolizumab may be resumed at grade 1 only if the investigator believes that the myocarditis has clinically resolved and the investigator has obtained written permission from the medical monitor to resume therapy.

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AE = adverse events; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = common terminology criteria for adverse events; irAE = immune-related adverse events

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

Subjects enrolled in the phase 1b who develop DLT during the DLT evaluation period will permanently discontinue pembrolizumab.

6.2.2.3 Rescue Medications and Supportive Care Guidelines for Pembrolizumab

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator including, but not limited, to the items outlined in Table 3.

Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined in Table 3. 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 in Table 3). Refer to Section 6.2.1.2 for dose modification.

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

6.2.2.3.1 Dose Modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab

Pembrolizumab may cause severe or life threatening infusion reaction including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab-associated infusion reaction are provided in Table 4.

Table 4. Pembrolizumab Infusion Reaction Dose Modification and 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 participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, non-steroidal anti-inflammatory drugs [NSAIDs], narcotics, intravenous [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 participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/hr to 50 mL/hr.). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment.	Participant may be premedicated 1.5 h (± 30 minutes) prior to infusion of _____ with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).

Table 4. Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilator 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 participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug treatment.	No subsequent dosing

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** 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

6.2.2.4 Diet and Other Considerations While Taking Pembrolizumab

6.2.2.4.1 Diet During Treatment With Pembrolizumab

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

6.2.2.4.2 Contraception Requirement for Pembrolizumab

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.

Subjects should be informed that taking pembrolizumab may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, men and women of reproductive potential must adhere to the contraception requirements (See Section 4.1.2, exclusion criteria 220 and 221) from the day of pembrolizumab initiation (or 14 days prior to the initiation of pembrolizumab for oral contraception) throughout the study period up to 120 days after the last dose of pembrolizumab. If there is any question that a subject of reproductive potential will not reliably comply with the requirements for contraception, that subject should not be enrolled into the study.

6.2.2.4.3 Use of Pembrolizumab in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study. The outcome of the pregnancy will be reported to Amgen and followed as described in Section 9.3 (Pregnancy and Lactation Reporting).

6.2.2.4.4 Use of Pembrolizumab in Nursing Women

It is unknown whether pembrolizumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, female subjects who are breast-feeding are not eligible for enrollment in this study.

6.3 Other Protocol-required Therapies

All other protocol-required therapies including, topical anesthetic or an injectable local anesthetic medications used for pretreatment of the talimogene laherparepvec/placebo injection site and oral or systemic steroids for management of pembrolizumab irAEs that are commercially available are not provided or reimbursed by Amgen (except if required by local regulation). The investigator will be responsible for obtaining supplies of these protocol-required therapies.

Additional details regarding these protocol-required therapies are provided in the IPIM.

6.4 Concomitant Therapy

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.8.

All prescription and nonprescription concomitant medication administered up to 28 days prior to enrollment/randomization, on an ongoing basis at enrollment/randomization, as well as changes in such concomitant medication, and, any new concomitant medication taken while the subject is on study, should be recorded on the appropriate CRF through 30 (+7) days after the last dose of talimogene laherparepvec/placebo or pembrolizumab, whichever is later. Concomitant medications administered 30 (+7) days after last dose of talimogene laherparepvec/placebo or pembrolizumab for serious adverse events should for recorded as defined in Section 9.2. The therapy name, indication, dose, unit, frequency, start date and stop date will be collected.

Investigators should use supportive care agents in compliance with their respective regional label. Investigators may not use supportive care agents as part of a separate clinical trial.

6.5 Other Treatment Procedures

Investigators may choose to resect lesions which become suitable for resection to render the subject free of macroscopic disease. Additionally, biopsies may be taken of cutaneous or subcutaneous lesions for tumor analysis during the study. However, resection of lesions may occur only following tumor assessment. If a subject undergoes resection of the lesion, the investigator or designee should notify the sponsor medical monitor as soon as possible. Tumor biopsies of the resected lesion are to be collected for [redacted] analysis.

Local radiation treatment to the site of bone and other metastasis will be permitted for palliative pain management at any time during the study. If a subject undergoes local radiation, the investigator or designee should notify the sponsor's medical monitor as soon as possible.

If a subject demonstrates evidence of new or worsening CNS metastases, all study treatments should be withheld and the investigator or designee should notify the sponsor's medical monitor as soon as possible. Subjects may be allowed to remain on study after discussion between the sponsor's medical monitor and the investigator to

determine the appropriateness of treatment resumption provided CNS lesions can be treated with stereotactic radiotherapy, Gamma Knife, or craniotomy. After approval is obtained from the sponsor's medical monitor, subjects may be allowed to reinitiate talimogene laherparepvec/placebo and/or pembrolizumab treatment per Sections 6.2.1.1 and 6.2.2.1, respectively, following stereotactic radiotherapy only when dosing of corticosteroid is below 1.5 mg dexamethasone, 10 mg prednisone or equivalent. If higher doses of corticosteroid are used, talimogene laherparepvec/placebo and/or pembrolizumab must be held until that dose level is reached during the period of steroid tapering.

6.6 Medical Devices

Medical devices (eg, 0.2 or 0.22 µm in-line filter made of polyethersulfone, intravenous administration set, infusion pump syringes, sterile needles, alcohol prep pads) that are commercially available are not usually provided or reimbursed by Amgen (except, for example, if required by local regulation). The investigator will be responsible for obtaining supplies of these devices.

6.7 Product Complaints

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of any investigational or non-investigational product(s) or device(s).

Any product complaint(s) associated with an investigational product(s) or non-investigational product(s) or device(s) supplied by Amgen are to be reported according to the instructions provided in the IPIM.

6.8 Excluded Treatments and/or Procedures During Study Period

Subjects must not use any of the following therapies during the screening or treatment period, unless indicated otherwise:

- other investigational agents or procedures
- concurrent experimental or approved antitumor therapies other than study drugs and radiation therapy required for palliation.
- immunosuppressive agents (with the exception of treatment for adverse events [see Sections 6.2.1.2, 6.2.2.2, and 6.2.2.3] and CNS metastases [see Section 6.5])
- any live vaccine therapies used for the prevention of infectious disease within 28 days prior to enrollment and during the treatment period
- antiherpetic drugs, other than if topically administered > 20 cm from a talimogene laherparepvec injection site

- any surgery or radiotherapy for melanoma (other than the exceptions noted in Section 6.5)
- Subjects must not schedule any elective surgeries (other than the exceptions noted in Section 6.5) 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 notify the sponsor's medical monitor as soon as possible. A subject may be allowed to resume study drugs if both the investigator and sponsor's medical monitor agree to restart study therapy.

The exclusion criteria describe other medications and procedures which are prohibited in this study (refer to Sections 4.1.2). The investigator or their designee must consult with the sponsor's medical monitor about subjects in the post-treatment follow up period who have not demonstrated confirmed disease progression, clinical instability (Section 3.1.3.1), or intolerance to pembrolizumab and/or talimogene laherparepvec prior to starting any experimental or approved antitumor therapies.

7. STUDY PROCEDURES

7.1 Schedule of Assessments

For Schedule of Assessments for phase 1b, phase 3 arm 1, and phase 3 arm 2 refer to Table 5 and Table 6, respectively.

Table 5. Schedule of Assessments for Phase 1b

	Screening			Study Treatment [d] (week number)																Follow-up	
Study Procedures	**≤ 28 days [a]**	**≤ 14 days [b]**	**≤ 72 hour [c]**	**-5**	**-2**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24 [z]**	**> 24 weeks[dd]**	**Safety [e]**	**Survival [f]**
General Assessments																					
Informed Consent	X																				
Review of Eligibility Criteria	X																				
Demographics, Medical, Surgical and Medication History	X																				
Recording of Concomitant Medication[i]	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	X[aa]
Vital Signs [g]	X			X	X	X		X		X		X		X		X		X	X	X	
Physical Exam Including Body Weight	X			X		X														X	
ECOG Performance Status	X			X		X														X	
12-lead electrocardiogram (ECG) [h]	X																			X	
Review of AEs and SAEs [i]	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	X[f]
Survival Assessment																					X
Local Laboratory Tests																					
Chemistry [j]		X		X	X	X		X		X		X		X		X		X	X	X	
Hematology [k]		X		X	X	X		X		X		X		X		X		X	X	X	
Total Immunoglobulin G (IgG)						X															
Urinalysis [cc]		X				X				X				X				X	X	X	
Lactate Dehydrogenase (LDH)		X																			
PT or INR and PTT or aPTT [bb]		X																			
T3, FT4, TSH [l]		X				X			X			X			X			X	X	X	
Urine or Serum Pregnancy Test [m]			X																	X	

Footnotes defined on last page of table.

Table 5. Schedule of Assessments for Phase 1b

	Screening			Study Treatment [d] (week number)																Follow-up	
Study Procedures	**≤ 28 days [a]**	**≤ 14 days [b]**	**≤ 72 hour [c]**	**-5**	**-2**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24 [z]**	**> 24 weeks[dd]**	**Safety [e]**	**Survival [f]**
Central Laboratory Tests																					
[redacted]																					
Swab of Herpetic Lesion for Real-Time Polymerase Chain Reaction (qPCR) [s]				Within 3 days of occurrence of suspected lesion of herpetic origin																	
Response Assessments																					
Clinical Tumor Assessment [t]	X					X						X						X	X	X	X
Photographs of Visible Cutaneous & Subcutaneous Tumor Lesions [u]	X					X						X						X	X	X	X
Radiographic (CT, PET/CT, MRI, or US) Scans & Tumor Assessment [v,w]	X					X						X						X	X	X	X
Treatment Administration																					
Talimogene laherparepvec [x]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Pembrolizumab [y]						X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Reporting Exposure to Talimogene Laherparepvec																					
Exposure of Healthcare Provider or Close Contact				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Footnotes defined on next page.

Note: Subjects enrolled in the phase 1b will receive talimogene laherparepvec 5 weeks before the initiation of pembrolizumab treatment. The start of talimogene laherparepvec will be defined as week -5. The start of pembrolizumab will be defined as week 0.

[a] Procedures to be performed ≤ 28 days prior to enrollment.

[b] Procedures to be performed ≤ 14 days prior to enrollment.

[c] Procedures to be performed ≤ 72 hours prior to enrollment.

[d] Talimogene laherparepvec treatment should begin as soon as possible after enrollment via IVRS but no later than 5 days after enrollment. During treatment, assessments and procedures will be performed within ± 3 days of the planned visit unless indicated otherwise.

[e] Safety follow-up will be performed approximately 30 (+7) days after the last dose of talimogene laherparepvec or the last dose of pembrolizumab, whichever is later. If an end of treatment decision occurs > 30 (+7) days after the last treatment date, then the safety follow-up should be performed as soon as possible (eg, within a week of the end of treatment decision).

[f] Subjects will be followed for survival every 12 weeks (± 28 days) from the date of the safety follow-up visit (or from the planned visit date if the safety follow-up visit does not occur) up to 60 months after the last subject randomized in phase 3. Subsequent cancer treatments for melanoma and talimogene laherparepvec-related adverse events will be collected as part of the long-term follow-up survival assessment.

[g] Vital signs (systolic/diastolic blood pressure, heart beat, respiration rate, and temperature) must be performed prior to the study treatment (talimogene laherparepvec and/or pembrolizumab) administration at week -5, -2, 0, then every 4 weeks, and at the safety follow-up.

[h] A single 12-lead ECG will be performed ≤ 28 days before enrollment and the safety follow-up visit.

[i] All SAEs that occur after the subject has signed the main informed consent through 90 (+7) days after the cessation of all study treatment or 30 (+7) days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, whichever is later, will be reported to Amgen and recorded in the CRF. SAEs must be reported to Amgen within 24 hours of the investigator knowledge of the event. All non-serious AEs that occur after first dose of talimogene laherparepvec or pembrolizumab and concomitant medications that are administered after enrollment through 30 (+7) days after the last dose of talimogene laherparepvec or the last dose of pembrolizumab, whichever is later, will be recorded in the case report form. Selected non-serious and serious AEs known as pembrolizumab Events of Clinical Interest that occurs after the first dose of pembrolizumab through 90 (+7) days after the last dose of pembrolizumab, or 30 (+7) days after initiation of a new anticancer therapy, whichever is earlier, must be reported to Amgen within 24 hours of the investigator's knowledge of the event regardless of attribution to pembrolizumab. AEs and concomitant medications should be assessed on an ongoing basis and recorded at each subject visit.

[j] Blood samples for chemistry will be collected at screening. During treatment blood samples will be collected prior to study treatment administration at day 1 (-3 days) of weeks -5, -2, 0, then every 4 weeks until end of study treatment. Results should be reviewed prior to the administration of scheduled dose of study drugs. Blood sample will also be collected at the safety follow-up visit (-3 days).

[k] Blood samples for hematology will be collected at screening. During treatment blood samples will be collected prior to study treatment administration at day 1 (-3 days) of weeks -5, -2, 0, then every 4 weeks until end of study treatment. Results should be reviewed prior to the administration of scheduled dose of study drugs. Blood sample will also be collected at the safety follow-up visit (-3 days).

[l] Blood samples for thyroid function tests (T3 [or FT3 per local standard], FT4, and TSH) will be collected at screening. Samples will be collected prior to study treatment administration on Day 1 (- 3 days) every 6 weeks until end of study treatment. Blood sample will also be collected at the safety follow-up visit (-3 days). Thyroid function tests must be collected, but if there are no symptoms of hypothyroidism or hyperthyroidism, study treatment can be initiated prior to the reporting of the laboratory results.

[m] Urine or serum pregnancy test to be performed on female of childbearing potential. A urine pregnancy test should be performed within 72 hours prior to enrollment and at the safety follow-up visit. If urine pregnancy test result is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Note: Additional (eg, monthly) on-treatment pregnancy testing should be conducted as required per local laws and regulations, where applicable.

[redacted]

[s] Swab of any lesion of herpetic origin for qPCR testing of talimogene laherparepvec DNA: Upon notification of a suspected herpetic lesion by the subject, the subject should be instructed to return to clinic within 3 days of the occurrence of reportable lesion suspected to be herpetic in origin such as cold sores or vesicles. The lesion should be evaluated by the investigator and swabbed if HSV infection is suspected. The sample will be collected, stored, and ultimately tested for the detection of talimogene laherparepvec DNA using qPCR.

[t] Clinical measurement of cutaneous, subcutaneous, and palpable nodal tumor lesions by caliper and response assessment per modified irRC (Appendix D). The screening clinical measurements must be done within 28 days prior to enrollment. During treatment, the clinical tumor assessments will performed independent of treatment cycle at week 0 (after 2 cycles of talimogene laherparepvec and prior to start of pembrolizumab), week 12 (+1 week) and every 12 weeks (+1 week) thereafter or more frequently if clinically indicated until confirmed PD per modified irRC (Appendix D) or start of new anticancer treatment. The schedule of clinical assessment of tumor lesions should not be adjusted for cycle initiation delays and performed according to the calendar. Response or progression should be by repeated clinical assessment ≥ 4 weeks after the first indication of response or progression. Tumor assessment is required at the safety follow up visit if the subject ended treatment prior to confirmed PD and has not had clinical tumor assessments performed within 4 weeks (+1 week) of the visit. For subjects who discontinued treatment for any reason other than confirmed PD, every effort should be made to complete clinical tumor assessments every 12 weeks (+1 week) or more frequently if clinically indicated during the long-term follow-up until documentation of confirmed PD per modified irRC (Appendix D), start of new anticancer treatment, if present, whichever occurs first. Note: When a lesion can be accurately evaluated by both radiographic imaging and clinical examination, radiographic imaging evaluations should be undertaken.

[u] Photographs of up to 5 (maximum 5 per organ) visible (ie, visible protrusion from skin surface) cutaneous and subcutaneous measurable tumor lesions which are selected as index lesions will be performed at screening within 28 days prior to enrollment. During treatment, the photographs of visible cutaneous and subcutaneous index tumor lesions and of new visible lesion cutaneous and subcutaneous lesions, if present, will **be** performed independent of treatment cycle at week 0 (after 2 cycles of talimogene laherparepvec and prior to start of pembrolizumab), week 12 (+1 week) and every 12 weeks (+1 week) thereafter or more frequently if clinically indicated until confirmed PD per modified irRC (Appendix D) or start of new anticancer treatment. The schedule of photograph of tumor lesions should not be adjusted for cycle initiation delays and performed according to the calendar. Response or progression should be confirmed by repeated photographs ≥ 4 weeks after the first indication of response or progression. Photographs of visible cutaneous and subcutaneous index tumor lesions and of new visible cutaneous and subcutaneous lesions, if present, is required at the safety follow up visit if the subject ended treatment prior to confirmed PD and has not had photographs performed within 4 weeks (+1 week) of the visit. For subjects who discontinued treatment for any reason other than PD, every effort should be made to complete photographs of visible cutaneous and subcutaneous index lesions and of new visible cutaneous and subcutaneous lesions, if present, every 12 weeks (+1 week) or more frequently if clinically indicated during the long-term follow-up until documentation of confirmed PD per modified irRC (Appendix D), start of new anticancer treatment, or end of study, whichever occurs first. The photographic images will collected and held for possible supportive retrospective review of tumor response by a blinded independent central review committee. Note: When a lesion can be accurately evaluated by both radiographic imaging and photographs, radiographic imaging evaluations should be undertaken.

[v] Radiographic imaging (CT, PET/CT, or MRI) of the chest, abdomen, and pelvis, and CT or MRI of the brain are required at screening. Tumor assessments must also include all other sites of disease. The screening scans must be done within 28 days prior to enrollment. During treatment, radiographic imaging (CT or MRI) of the abdomen, pelvis, and chest, along with tumor assessments of all other sites of disease, (and CT or MRI of the brain if a subject has symptoms or signs suggestive of CNS metastases), will be performed independent of treatment cycle at week 0 (after 2 cycles of talimogene laherparepvec and prior to start of pembrolizumab), week 12 (+1 week), and then every 12 weeks (+1 week) or more frequently if clinically indicated until confirmed PD per modified irRC (Appendix D) or start of new anticancer treatment. Imaging should not be adjusted for cycle initiation delays and performed according to the calendar. The imaging modality selected (eg, CT or MRI) should remain constant for any individual subject. Response or progression should be confirmed by repeated radiographic imaging ≥ 4 weeks after the first indication of response or progression. Radiographic imaging is required at the safety follow up visit if the subject ended treatment prior to confirmed PD and has not had radiographic tumor imaging performed within 4 weeks (+1 week) of the visit. For subjects who discontinued treatment for any reason other than confirmed PD, every effort should be made to complete radiographic assessments every 12 weeks (+1 week) or more frequently if clinically indicated during the long-term follow-up until documentation of confirmed PD per modified irRC (Appendix D), start of new anticancer therapy, or end of study, whichever occurs first. Subjects who have reached a confirmed CR may increase their interval of radiographic assessments up to 6 months after the first 2 years beyond confirmed CR and up to 12 months after the first 5 years beyond confirmed CR as long as CR is maintained. The radiographic images will be collected and held for possible supportive retrospective review of tumor response by a blinded independent central review committee.

[w] Response (CR, or PR) or PD to be confirmed by second consecutive response assessment no less than 4 weeks from the date of the first documented response or PD.

[x] Talimogene laherparepvec will be administered to subjects randomized on day 1 of week -5, day 1 of week -2 (+3 days), day 1 of week 0 (± 3 days) and every 2 weeks (± 3 days) thereafter. The initial dose of talimogene laherparepvec is up to 4.0 mL of 10^6 PFU/mL. Subsequent doses of talimogene laherparepvec are up to 4.0 mL of 10^8 PFU/mL. Dosing of talimogene laherparepvec should be continued until CR, disappearance of injected lesion, confirmed PD per modified irRC (Appendix D), intolerance of study treatment, 24 months from the first dose of talimogene laherparepvec, or end of study, whichever occurs first. 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. Therefore, dosing should be continued provided that the subject has no evidence of confirmed PD per modified irRC (Appendix D) and is able to tolerate the treatment. Assessments and procedures are to be performed within 3 days of the planned visit and results available prior to study drug administration, unless otherwise specified. It is recommended that dosing occur on the same day of the week (eg, if first dose is administered on a Monday, all subsequent doses should be administered on a Monday), however, a ± 3 day dosing window is allowed.

[y] Pembrolizumab will be administered intravenously to subjects randomized at a dose of 200 mg every 2 weeks (± 3-days) starting at day 1 of week 0 (at the time of the third dose of talimogene laherparepvec) until confirmed PD per modified irRC (Appendix D), intolerance to pembrolizumab, 24 months from the first dose of pembrolizumab, or end of study, whichever occurs first. When talimogene laherparepvec and pembrolizumab are administered on the same day, talimogene laherparepvec should be administered first, if possible.

[z] Repeat week 24 procedures and assessments until end of study treatment unless otherwise indicated.

[aa] Only subsequent treatment for melanoma will be recorded.

[bb] Blood sample for coagulation will be collected at screening. During treatment, blood samples should be collected for coagulation as clinically indicated.

[cc] Urine samples for urinalysis will be collected at screening. During treatment urine samples will be collected prior to study treatment administration at day 1 of weeks 0, 8, 16 then every 8 weeks until end of study treatment. Results should be reviewed prior to the administration of scheduled dose of study drugs. Urine sample will also be collected at the safety follow-up visit. Reflexive microscopy should be obtained for any abnormal urinalysis result.

[dd] > 24 study treatment week number pertains to all the study procedures required beyond week 24. To determine the frequency of each study procedure, please refer to the footnote associated with that particular study procedure.

Table 6. Schedule of Assessments for Phase 3 – Arms 1 and 2

	Screening			Study Treatment [d] (week number)												Follow-up	
Study Procedures	**≤ 28 days [a]**	**≤ 14 days [b]**	**≤ 72 hour [c]**	**0**	**3**	**5**	**6**	**7**	**9**	**12**	**15**	**18**	**21**	**24[y]**	**> 24 weeks[ee]**	**Safety [e]**	**Survival [f]**
General Assessments																	
Informed Consent	X																
Review of Eligibility Criteria	X																
Demographics, Medical, Surgical and Medication History	X																
Recording of Concomitant Medication [i]	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	X[z]
Vital Signs [g]	X			X	X		X			X		X		X	X	X	
Physical Exam Including Body Weight	X			X												X	
ECOG Performance Status	X			X												X	
12-lead ECG [h]	X															X	
Review of AEs and SAEs [i]	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	X[f]
Survival Assessment																	X
QLQ-C30 Questionnaire [cc]				X	X		X		X	X		X		X	X	X	X
EQ-5D-3L [dd]				X	X		X		X	X		X		X	X	X	X
Local Laboratory Tests																	
Chemistry [j]		X		X	X		X			X		X		X	X	X	
Hematology [k]		X		X	X		X			X		X		X	X	X	
Total Immunoglobulin G (IgG)				X													
Urinalysis [bb]		X		X			X			X		X		X	X	X	
LDH		X		X	X		X			X		X		X	X	X	
PT or INR and PTT or aPTT [aa]		X															
T3, FT4, TSH [l]		X		X			X			X		X		X	X	X	
Urine or Serum Pregnancy Test [m]			X													X	

Footnotes defined on last page of table.

Table 6. Schedule of Assessments for Phase 3 – Arms 1 and 2

	Screening			Study Treatment [d] (week number)												Follow-up	
Study Procedures	**≤ 28 days [a]**	**≤ 14 days [b]**	**≤ 72 hour [c]**	**0**	**3**	**5**	**6**	**7**	**9**	**12**	**15**	**18**	**21**	**24[y]**	**> 24 weeks[ee]**	**Safety [e]**	**Survival [f]**
Central Laboratory Tests																	
[redacted]																	
Swab of Herpetic Lesion for qPCR [s]				Within 3 days of occurrence of suspected lesion of herpetic origin													
Response Assessments																	
Photographs of Visible Cutaneous & Subcutaneous Tumor Lesions [t]	X									X				X	X	X	X
Radiographic (CT, PET/CT, or MRI) Scans & Tumor Assessment [u,v]	X									X				X	X	X	X
Treatment Administration																	
Talimogene laherparepvec or placebo[w]				X	X	X		X	X	X	X	X	X	X	X		
Pembrolizumab [x]				X	X		X		X	X	X	X	X	X	X		
Reporting Exposure to Talimogene Laherparepvec or Placebo																	
Exposure of Healthcare Provider or Close Contact				X	X	X	X	X	X	X	X	X	X	X	X	X	

Footnotes defined on next page.

[a] Procedures to be performed ≤ 28 days prior to enrollment.
[b] Procedures to be performed ≤ 14 days prior to enrollment.
[c] Procedures to be performed ≤ 72 hours prior to enrollment.
[d] Treatment should begin as soon as possible after randomization via IVRS but no later than 5 days after randomization. During treatment, assessments and procedures will be performed within ± 3 days of the planned visit unless indicated otherwise.
[e] Safety follow-up will be performed approximately 30 (+7) days after the last dose of talimogene laherparepvec or placebo or the last dose of pembrolizumab, whichever is later. If an end of treatment decision occurs > 30 (+7) days after the last treatment date, then the safety follow-up should be performed as soon as possible (eg, within a week of the end of treatment decision).
[f] Subjects will be followed for survival every 12 weeks (± 28 days) from the date of the safety follow-up visit (or from the planned visit date if the safety follow-up visit does not occur) until death, subject withdraws full consent, or up to 60 months after the last subjects randomized in phase 3. Subsequent cancer treatments for melanoma and any injected investigational product-related adverse events and EQ-5D-3L (every 12 weeks) will be collected as part of the long-term follow-up survival assessment.
[g] Vital signs (systolic/diastolic blood pressure, heart beat, respiration rate, and temperature) must be performed prior to the study treatment (talimogene laherparepvec and/or pembrolizumab) administration at week 0, 3, 6, 12 and every 6 weeks thereafter, and at the safety follow-up.
[h] A single 12-lead ECG will be performed ≤ 28 days before enrollment and the safety follow-up visit.
[i] All SAEs that occur during screening through 90 (+7) days after the cessation of all study treatment or 30 (+7) days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, will be reported to Amgen and recorded in the CRF. SAEs must be reported to Amgen within 24 hours of the investigator knowledge of the event. All non-serious AEs that occur after first dose of talimogene laherparepvec or pembrolizumab and concomitant medications that are administered after randomization through 30 (+7) days after the last dose of talimogene laherparepvec or placebo or the last dose of pembrolizumab, whichever is later, will be recorded in the CRF. Selected non-serious and serious AEs known as pembrolizumab Events of Clinical Interest that occur after the first dose of pembrolizumab through the safety follow up period, or 30 (+7) days after initiation of a new anticancer therapy, whichever is earlier, must be reported to Amgen within 24 hours of the investigator's knowledge of the event regardless of attribution to pembrolizumab. AEs and concomitant medications should be assessed on an ongoing basis and recorded at each subject visit. Talimogene laherparepvec/placebo-related AEs will be collected following the long term safety follow-up period until end of study.
[j] Blood samples for chemistry will be collected at screening. During treatment blood samples will be collected prior to study treatment administration at day 1 (-3 days) of week 0, day 1 of week 3, 6, 12 and then every 6 weeks until end of study treatment. Results should be reviewed prior to the administration of scheduled dose of study drugs. Blood sample will also be collected at the safety follow-up visit (-3 days).
[k] Blood samples for hematology will be collected at screening. During treatment blood samples will be collected prior to study treatment administration at day 1 (-3 days) of week 0, day 1 of week 3, 6, 12 and then every 6 weeks until end of study treatment. Results should be reviewed prior to the administration of scheduled dose of study drugs. Blood sample will also be collected at the safety follow-up visit (-3 days).
[l] Blood samples for thyroid function tests (T3 [or FT3 per local standard], FT4, and TSH) will be collected at screening. Samples will be collected prior to study treatment administration on day 1 (- 3 days) every 6 weeks until end of study treatment. Blood sample will also be collected at the safety follow-up visit (-3 days). Thyroid function tests must be collected, but if there are no symptoms of hypothyroidism or hyperthyroidism, study treatment can be initiated prior to the reporting of the laboratory results.
[m] Urine or serum pregnancy test to be performed on female of childbearing potential. A urine pregnancy test should be performed within 72 hours prior to enrollment and at the safety follow-up. If urine pregnancy test result is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Note: Additional (eg, monthly) on-treatment pregnancy testing should be conducted as required per local laws and regulations, where applicable.

[s] Swab of any lesion of herpetic origin for qPCR testing of talimogene laherparepvec DNA: Upon notification of a suspected herpetic lesion by the subject, the subject should be instructed to return to clinic within 3 days of the occurrence of reportable lesion suspected to be herpetic in origin such as cold sores or vesicles. The lesion should be evaluated by the investigator and swabbed if HSV infection is suspected. The sample will be collected, stored, and ultimately tested for the detection of talimogene laherparepvec DNA using qPCR.

[t] Photographs of all visible (ie, visible protrusion from skin surface) cutaneous and subcutaneous tumor lesions not detectable on radiographic imaging must be performed at screening within 28 days prior to enrollment for the purposes of documentation of baseline lesion data. It is critical that baseline photography is captured for subjects with visible cutaneous and subcutaneous tumor lesions in order to allow for follow up of these lesions during the treatment phase. During treatment, the photographs of all visible cutaneous and subcutaneous tumor lesions not detectable on radiographic imaging, including new visible lesion cutaneous and subcutaneous lesions, if present, must be performed independent of treatment cycle at Day 1 of week 12 (+1 week) and every 12 weeks (+1 week) thereafter or more frequently if clinically indicated until confirmed iPD per modified irRC-RECIST (Appendix F) or start of new anticancer treatment. Photographs must also be taken for previously visible cutaneous and subcutaneous tumor lesions that have resolved at subsequent tumor assessment visits. The schedule of photograph of tumor lesions should not be adjusted for cycle initiation delays and performed according to the calendar. Response or progression should be confirmed by repeated photographs ≥ 4 weeks after the first indication of response or progression. Photographs of all visible cutaneous and subcutaneous tumor lesions not detectable on radiographic imaging, including new visible cutaneous and subcutaneous lesions, if present, is required at the safety follow-up visit if the subject ended treatment prior to confirmed iPD and has not had photographs performed within 4 weeks (+1 week) of the visit. For subjects who discontinued treatment for any reason other than iPD, every effort should be made to complete photographs of all visible cutaneous and subcutaneous lesions not detectable on radiographic imaging, including new visible cutaneous and subcutaneous lesions, if present, every 12 weeks (+1 week) or more frequently if clinically indicated during the long-term follow-up until documentation of confirmed iPD per modified irRC-RECIST (Appendix F), start of new anticancer treatment, or end of study, whichever occurs first. Subjects who have reached a confirmed iCR may increase their interval of radiographic assessments up to 6 months after the first 2 years beyond confirmed iCR and up to 12 months after the first 5 years beyond confirmed iCR as long as iCR is maintained. The photographic images will be collected for review of tumor response by a blinded independent central review committee. Photographed lesions not appearing on radiographic imaging should only be considered non-target lesions and not target lesions. Note: When a lesion can be accurately evaluated by both radiographic imaging and photographs, radiographic imaging evaluations must be undertaken. When a lesion/lesions can not be evaluated by radiographic imaging, but can be accurately evaluated by both clinical examination and photographs, photographs must be undertaken.

[u] Radiographic imaging (CT, PET/CT, or MRI) of the chest, abdomen, and pelvis, and CT or MRI of the brain are required at screening. Tumor assessments must also include all other sites of disease. The screening scans must be done within 28 days prior to enrollment. During treatment, radiographic imaging (CT or MRI) of the abdomen, pelvis, and chest, along with tumor assessments of all other sites of disease, (and CT or MRI of the brain if a subject has symptoms or signs suggestive of CNS metastases), will be performed independent of treatment cycle at week 12 (+1 week), and then every 12 weeks (+1 week) or more frequently if clinically indicated until confirmed iPD per modified irRC-RECIST (Appendix F) or start of new anticancer treatment. Imaging should not be adjusted for cycle initiation delays and performed according to the calendar. The imaging modality selected (eg, CT or MRI) should remain constant for any individual subject. Response or progression should be confirmed by repeated radiographic imaging ≥ 4 weeks after the first indication of response or progression. Radiographic imaging is required at the safety follow up visit if the subject ended treatment prior to confirmed iPD and has not had radiographic tumor imaging performed within 4 weeks (+1 week) of the visit. For subjects who discontinued treatment for any reason other than confirmed iPD, every effort should be made to complete radiographic assessments every 12 weeks (+1 week) or more frequently if clinically indicated during the long-term follow-up until documentation of confirmed iPD per modified irRC-RECIST (Appendix F), start of new anticancer therapy, or end of study whichever occurs first. The radiographic images will be collected for review of tumor response by a blinded independent central review committee.

[v] Response (iCR, or iPR) or iPD to be confirmed by second consecutive response assessment no less than 4 weeks from the date of the first documented response or PD.

[w] Talimogene laherparepvec or placebo will be administered on day 1 of week 0, day 1 of week 3 (+3 days), then every 2 weeks (± 3 days) until week 9, and thereafter every 3 weeks (± 3 days) synchronously with pembrolizumab. The initial dose of talimogene laherparepvec is up to 4.0 mL of 10^6 PFU/mL. Subsequent doses of talimogene laherparepvec are up to 4.0 mL of 10^8 PFU/mL. Dosing of talimogene laherparepvec or placebo should be continued until CR, disappearance of injected lesion, documented confirmed iPD per modified irRC-RECIST (Appendix F), intolerance of study treatment, 24 months from the first dose of talimogene laherparepvec or placebo, or end of study, whichever occurs first. 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. Therefore, dosing should be continued provided that the subject has no evidence of confirmed iPD per modified irRC-RECIST (Appendix F) and is able to tolerate the treatment. Assessments and procedures are to be performed within 3 days of the planned visit and results available prior to study drug administration, unless otherwise specified. It is recommended that dosing occur on the same day of the week (eg, if first dose is administered on a Monday, all subsequent doses should be administered on a Monday), however, a ± 3 day dosing window is allowed.
[x] Pembrolizumab will be administered at a dose of 200 mg starting at day 1 of week 0, day 1 of week 3 (+3 days), and every 3 weeks (± 3 days) thereafter until documented confirmed iPD per modified irRC-RECIST (Appendix F), intolerance to pembrolizumab, 24 months from the first dose of pembrolizumab, or end of study, whichever occurs first. When talimogene laherparepvec or placebo injections and pembrolizumab are administered on the same day, talimogene laherparepvec or placebo should be administered first, if possible.
[y] Repeat week 24 procedures and assessments until end of study treatment, unless otherwise indicated.
[z] Only subsequent treatment for melanoma will be recorded.
[aa] Blood sample for coagulation will be collected at screening. During treatment, blood samples should be collected for coagulation as clinically indicated.
[bb] Urine samples for urinalysis will be collected at screening. During treatment urine samples will be collected prior to study treatment administration at day 1 of weeks 0, 6, 12, 18, 24, then every 12 weeks until end of study treatment. Results should be reviewed prior to the administration of scheduled dose of study drugs. Urine sample will also be collected at the safety follow-up visit. Reflexive microscopy should be obtained for any abnormal urinalysis result.
[cc] The QLQ-C30 questionnaire will be completed prior to study treatment administration at day 1 of weeks 0, 3, 6, 9, 12, then every 6 weeks until end of study treatment, and at the safety follow-up visit. For subjects who discontinued treatment for any reason other than confirmed PD, every effort should be made to complete the EQ-5D-3L and QLQ-C30 questionnaires every 12 weeks (+1 week) during the long-term follow-up until documentation of confirmed iPD per modified irRC-RECIST (Appendix F), start of new anticancer therapy, or end of study whichever occurs first.
[dd] The EQ-5D-3L questionnaire will be completed prior to study treatment administration at day 1 of weeks 0, 3, 6, 9, and 12, and then every 6 weeks, and at the time of disease progression (confirmed iPD or unconfirmed iPD with clinical deterioration), safety follow-up, and then every 12 weeks (± 1 to 3 weeks) thereafter during the long term follow-up visits. If patients are too ill to self-complete, proxy completion by a named person (eg, a relative or health care provider) should be performed. At least 2 assessments completed by both the patient and the named proxy-respondent at the same time should be made (eg, at a pre-progression visit [ie, week 0] and the first assessment after disease progression).
[ee] > 24 study treatment week number pertains to all the study procedures required beyond week 24. To determine the frequency of each study procedure, please refer to the footnote associated with that particular study procedure.

Refer to the applicable supplemental laboratory and imaging manuals for detailed collection and handling procedures.

7.2 General Study Procedures

A signed and dated IRB-approved informed consent must be obtained before any study-specific procedures are performed. Procedures that are part of routine care are not considered study-specific procedures and may be used at screening to determine eligibility. All subjects will be screened for eligibility before enrollment. Only eligible subjects will be enrolled into the study.

During treatment, assessments and procedures can be performed within 3 days of the planned visit. It is recommended that dosing occur on the same day of the week (eg, if first dose is administered on Monday, all subsequent doses should be administered on a Monday), however a ± 3-day dosing and study procedure window is allowed.

The following laboratory analytes in Table 7 will be assessed at various times throughout the study.

Table 7. Laboratory Analytes

Chemistry	Coagulation	Thyroid Function	Hematology	Other Labs
Sodium Potassium Chloride Calcium Magnesium Phosphorus Uric acid Total protein Albumin BUN/Urea Creatinine Total bilirubin Alkaline-phosphatase AST ALT Glucose	PT or INR PTT or aPTT	TSH T3 (or FT3 per local standard) FT4	RBC Hemoglobin Hematocrit Platelets WBC Differential* • Neutrophils • Eosinophils • Basophils • Lymphocytes • Monocytes	Pregnancy LDH Urinalysis • Blood • Glucose • Protein • Specific gravity • Microscopic exam (only reflexively for abnormal urinalysis results) qPCR for talimogene laherparepvec DNA HSV-1 antibody Anti-pembrolizumab antibody Pembrolizumab PK [redacted] Total IgG • Blood • Archived tumor tissue [redacted]

* 3-part differential if 5-part unable to be performed

All tests (except for qPCR, antibody, PK, and [redacted] are to be performed at a local laboratory and test results are to be fully and routinely recorded on the CRFs. Missed tests that are not done must be reported as such on the CRFs. The qPCR, antibody, PK and [redacted] will be performed at a central laboratory and results will not be recorded on the CRFs.

Other on-study tests deemed necessary as part of standard of care or as required by local laws and regulations may be performed at the Investigator's discretion as long as the subject remains active in the clinical study.

Where required by local laws or regulations, additional assessments are defined in a country-specific protocol supplement at the end of the Appendix Section of protocol.

7.2.1 Screening, Enrollment (Phase 1b) and Randomization (Phase 3)

The following procedures are to be completed during the screening period within 28 days of enrollment/randomization (unless otherwise noted) at time points designated in the Schedule of Assessments (Table 5 and Table 6):

Phase 1b and 3:

- Confirmation that the Informed Consent Form has been signed
- Review of eligibility criteria
- Demographic data including sex, age or date of birth, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness.
- Vital signs (systolic/diastolic blood pressure, heart rate, respiration rate, temperature): Subject must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The position selected for a subject should be the same that is used throughout the study and documented on the vital sign CRF. Record all measurements on the vital signs CRF.
- Medical, surgical and medication history
- Physical examination including body weight as per standard of care
- Documentation of concomitant medications
- ECOG performance status assessment
- A 12-lead electrocardiogram (ECG): The ECG must include the following measurements: heart rate, PR, QRS, QT and QTc intervals. Subject must be in supine position in a rested and calm state for at least 5 minutes before ECG assessment is conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The investigator or designated site physician will review all ECGs. Once signed, the original ECG tracing will be retained with the subject's source documents. At the request of the sponsor, a copy of the original ECG will be made available to Amgen.

- Local Laboratory Assessments
  - within ≤ 14 days prior to enrollment/randomization
    - hematology panel: hemoglobin, hematocrit, white blood cell (WBC) count with 5-part differential (3-part differential if 5-part unable to be performed), red blood cell (RBC) count, platelets
    - chemistry panel: sodium, potassium, chloride, calcium, magnesium, phosphorous, uric acid, total protein, albumin, blood urea nitrogen (BUN), creatinine, total bilirubin, alkaline phosphatase, AST, ALT, glucose
    - LDH
    - coagulation: PT or INR and PTT or aPTT
    - thyroid function tests: T3 (or FT3 per local standard), FT4, TSH
    - urinalysis (blood, glucose, protein, specific gravity) and reflexive microscopic exam only for any abnormal urinalysis result
    - serum or urine pregnancy test for female subjects of childbearing potential (urine pregnancy test should be performed within 72 hours prior to enrollment).
- Radiographic tumor imaging (including CT scan, positron emission tomography [PET]/CT scan, magnetic resonance imaging [MRI]) of the chest, abdomen, pelvis, and all other sites of disease, and CT scan or MRI of the brain, to be used as baseline imaging
- Recording of serious adverse events that occur after subject signs informed consent. Serious adverse events will be reported to Amgen within 24 hours following the investigator's knowledge of the event
- Review of inclusion and exclusion criteria
- Registration and/or randomization in IVRS

<u>Phase 1b only:</u>

- Clinical tumor assessments, including clinical measurement of cutaneous, subcutaneous, and palpable nodal tumor lesions by caliper to be used as baseline assessment. Note: When a tumor lesion can be accurately evaluated by both, radiographic imaging and clinical examination, radiographic imaging evaluations should be undertaken.
- Photographs of visible (ie, visible protrusion from skin surface) cutaneous and subcutaneous tumor lesions:
  - Photographs of visible cutaneous and subcutaneous measurable tumor lesions (up to 5; maximum 5 per organ) which are selected as index lesions will be performed.
  - Note: When a tumor lesion can be accurately evaluated by both, radiographic imaging and photographs, radiographic imaging evaluations should be undertaken.

- Tumor biopsy for PD-L1 expression, $BRAF^{V600}$ mutation, and [redacted] analyses:
  - One lesion will be biopsied within 28 days prior to enrollment (archived formalin-fixed paraffin-embedded tumor biopsy tissue may be substituted if biopsy was performed within 3 months prior to Day 1, and no systemic anticancer therapies were given since the archival biopsy was performed).

    Subjects with an unevaluable archival sample for PD-L1 expression testing and $BRAF^{V600}$ mutation testing may obtain a new biopsy and subjects with an unevaluable newly obtained biopsy may undergo re-biopsy at the discretion of the investigator. If repeat sample is also unevaluable and the subject is otherwise eligible, the investigator may enroll the subject with or without a second re-biopsy.

    Subjects with an unevaluable newly obtained biopsy may undergo re-biopsy at the discretion of the investigator. If the subject is ready to be randomized and treated after re-biopsy, randomization and start of treatment may proceed.

    In the case of an unevaluable BRAF mutation status, the subject must have LDH < ULN, no clinically significant tumor related symptoms in the judgment of the investigator, and have absence of rapidly progressing metastatic melanoma in the judgment of the investigator.

<u>Phase 3 only:</u>

- Archived tumor tissue for PD-L1 expression, $BRAF^{V600}$ mutation testing, and [redacted] analyses:
  - PD-L1 expression testing: Subject must submit the tumor sample during screening for PD-L1 expression testing at a central laboratory. Subjects with an unevaluable archival sample may obtain a new biopsy during screening as described below.
  - $BRAF^{V600}$ mutation testing must be performed prior to randomization if a subject meets any of the following criteria:
    - LDH > ULN
    - Presence of clinically significant tumor related symptoms in the judgment of the investigator
    - Presence of rapidly progressing metastatic melanoma in the judgment of the investigator
  - $BRAF^{V600}$ mutation testing may be obtained in a number of ways as listed below:
    - Previously Known $BRAF^{V600}$ Tumor Status: $BRAF^{V600}$ tumor status result, obtained prior to screening for this study, from a local laboratory will be acceptable. The local laboratory report supporting the local $BRAF^{V600}$ tumor testing result should be available at the site within 4 weeks prior to randomization if the subject meets any of the above criteria or within 4 weeks after randomization if the subject does not meet any of the above criteria.

  - Previously Unknown $BRAF^{V600}$ Tumor Status: Archived formalin-fixed paraffin-embedded tumor tissue (block or unstained tumor slide) from either the primary tumor or a metastatic lesion should be analyzed at a local laboratory or submitted to the central laboratory within 4 weeks prior to randomization if the subject meets any of the above criteria or within 4 weeks after randomization if the subject does not meet any of the above criteria. Subjects with an unevaluable archival sample for $BRAF^{V600}$ testing may obtain a new biopsy during screening as described below.

- Tumor biopsy for PD-L1 expression, $BRAF^{V600}$ mutation, and [redacted] analyses:
  - One lesion will be biopsied within 28 days prior to enrollment (archived formalin-fixed paraffin-embedded tumor biopsy tissue may be substituted if biopsy was performed within 3 months prior to day 1, and no systemic anticancer therapies were given since the biopsy was done).

    Subjects with an unevaluable archival sample for PD-L1 expression testing and $BRAF^{V600}$ mutation testing may obtain a new biopsy. If the subject is ready to be randomized and treated after obtaining the new biopsy, randomization and start of treatment may proceed.

    Subjects with an unevaluable newly obtained biopsy may undergo re-biopsy at the discretion of the investigator. If the subject is ready to be randomized and treated after re-biopsy, randomization and start of treatment may proceed.

    In the case of an unevaluable BRAF mutation status, the subject must have LDH less than ULN, no clinically significant tumor related symptoms in the judgment of the investigator, and have absence of rapidly progressing metastatic melanoma in the judgment of the investigator.
- Local laboratory assessments
  - Chemistry assessments: BUN/urea
- Photographs of visible (ie, visible protrusion from skin surface) cutaneous and subcutaneous tumor lesions:
  - Photographs of all visible cutaneous and subcutaneous tumor lesions not detectable on radiographic imaging must be performed for the purposes of baseline tumor lesion documentation to be used for subsequent tumor assessments.
  - Note: When a tumor lesion can be accurately evaluated by both, radiographic imaging and photographs, radiographic imaging evaluations must be undertaken. When a lesion/lesions can not be evaluated by radiographic imaging, but can be accurately evaluated by both clinical examination and photographs, photographs must be undertaken.

7.2.2 Treatment Period

Treatment begins when the first dose of protocol-required therapies is administered to a subject.

The following procedures will be completed during the treatment period at the times designated in the Schedule of Assessments (Table 5 and Table 6). Study treatment should begin as soon as possible after enrollment via IVRS but no later than 5 days after

enrollment/randomization. Study treatment is to be administered after all other procedures are completed, unless otherwise stated during each visit that it is required.

Phase 1b and 3:

- Local laboratory assessments: Screening laboratory values may be used for treatment initiation assessment if completed within 3 days of study treatment initiation. On treatment tests can be performed within 3 days of the planned visit. Results should be reviewed prior to the administration of study treatment.
  - Coagulation: PT or INR and PTT or aPTT – as clinically indicated
  - Serum or urine pregnancy test for female subjects of childbearing potential: Additional (eg, monthly) on-treatment pregnancy testing should be conducted as required per local laws and regulations, where applicable.
- Central laboratory assessments:
  - Swab of cold sore, vesicles and other lesions suspected to be herpetic in origin (if any) for qPCR testing of talimogene laherparepvec DNA:
    - Upon notification of a suspected herpetic lesion by the subject, the subject should return to the clinic within 3 days of the occurrence of a reportable lesion suspected to be herpetic in origin. The lesion should be evaluated by the investigator and swabbed if HSV infection is suspected. A qPCR analysis will be performed on the swab sample to evaluate whether the talimogene laherparepvec DNA is detectable in the sample.
- Recording of adverse events at each visit
- Recording of serious adverse events at each visit. Serious adverse events will be reported to Amgen within 24 hours following the investigator's knowledge of the event.
- For subject treated with pembrolizumab: Selected non-serious and serious adverse events known as pembrolizumab Events of Clinical Interest must be reported to Amgen within 24 hours of the investigator's knowledge of the event regardless of attribution to pembrolizumab (see Section 9.5)
- Documentation of concomitant medications at each visit

Phase 1b:

- Vital signs (systolic/diastolic blood pressure, heart rate, respiration rate, temperature): Subject must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position possible. The position selected for a subject should be the same that is used throughout the study and be documented on the vital signs CRF.
  - day 1 of weeks -5, -2, 0, 4, 8, 12 and then every 4 weeks until end of study treatment
- Physical examination including body weight, as per standard of care
  - day 1 of weeks -5 and 0

- ECOG performance status
  - day 1 of weeks -5 and 0
- Local laboratory assessments: Screening laboratory values may be used for treatment initiation assessment if completed within 3 days of study treatment initiation. On treatment tests can be performed within 3 days of the planned visit. Results should be reviewed prior to the administration of study treatment.
  - Hematology panel: hemoglobin, hematocrit, WBC with 5-part differential (3-part differential if 5-part unable to be performed), RBC, platelet
    - day 1 of weeks -5, -2, 0, 4, 8, 12 and then every 4 weeks until end of study treatment
  - Chemistry panel: sodium, potassium, chloride, calcium, magnesium, phosphorus, uric acid, total protein, albumin, BUN, creatinine, total bilirubin, alkaline phosphatase, AST, ALT, glucose
    - day 1 of weeks -5, -2, 0, 4, 8, 12 and then every 4 weeks until the end of study treatment
  - Blood sample for total immunoglobulin G (IgG)
    - day 1 of week 0
  - Thyroid function tests: T3 (or FT3 per local standard), FT4, TSH
    - day 1 every 6 weeks until the end of study treatment
  - Urinalysis (blood, glucose, protein, specific gravity) and reflexive microscopic exam only for any abnormal urinalysis result
    - day 1 of weeks 0, 8, 16, week 24 and then every 8 weeks until end of study treatment
- Central laboratory assessments:

  - Blood for anti-pembrolizumab antibody (immunogenicity):
    - day 1 of weeks 0, 2, 8, 16, 24 and every 12 weeks (6 cycles) starting with week 36.
    - Note: All samples should be drawn within 24 hours before infusion of pembrolizumab and at the same time as the pre-dose trough blood collection for the PK sample.

  - Blood for PK of pembrolizumab:
    - pre-dose trough and post-dose peak PK samples will be collected on day 1 of week 0. A one-time PK sample should be drawn between 48 to 168 hours after week 0. Pre-dose trough samples only will be collected at week 2, 8, 16, 24 every 12 weeks (6 cycles) starting with week 36.
    - Note: All trough samples should be drawn within 24 hours before infusion of pembrolizumab. Peak sample should be drawn within 30 minutes after the end of the infusion.

- Archived tumor tissue for $BRAF^{V600}$ mutation testing:
  - $BRAF^{V600}$ mutation testing for may be obtained in a number of ways as listed below:
    - Previously Known $BRAF^{V600}$ Tumor Status: $BRAF^{V600}$ tumor status result, obtained prior to screening for this study, from a local laboratory will be acceptable. The local laboratory report supporting the local $BRAF^{V600}$ tumor testing result should be available at the site within 4 weeks after enrollment.
    - Previously Unknown $BRAF^{V600}$ Tumor Status: Archived formalin-fixed paraffin-embedded tumor tissue (block or unstained tumor slide) from either the primary tumor or a metastatic lesion should be analyzed at a local laboratory or submitted to the central laboratory within 4 weeks after enrollment.

[redacted]

- Radiographic tumor imaging assessments must include CT scan, PET/CT, or MRI of the abdomen, pelvis, and chest and all other sites of disease. In addition, CT scan or MRI of the brain will only be performed if signs or symptoms suggestive of CNS metastasis are present. Imaging will be performed independent of treatment cycle at day 1 of week 0, day 1 of week 12 (+1 week), and then every 12 weeks (+1 week) or more frequently if clinically indicated until confirmed PD per modified irRC (Appendix D), or start of new anticancer treatment. Imaging should not be adjusted for cycle initiation delays and performed according to the calendar. The imaging modality selected (eg, CT or MRI) should remain constant for any individual subject.
- Photographs of visible cutaneous and subcutaneous:
  - Photographs of visible cutaneous and subcutaneous index tumor lesions and of new visible lesion cutaneous and subcutaneous, if present, will be performed independent of treatment cycle at day 1 of week 0, day 1 of week 12 (+1 week) and every 12 weeks (+1 week) thereafter or more frequently if clinically indicated until confirmed PD per modified irRC (Appendix D) or start of new anticancer treatment. The scheduled photography of tumor lesions should not be adjusted for cycle initiation delays and performed according to the calendar.
  - Note: When a tumor lesion can be accurately evaluated by both, radiographic imaging and photographs, radiographic imaging evaluations should be undertaken.

- Clinical tumor assessments must include clinical measurement of cutaneous, subcutaneous, or palpable nodal tumor lesions by caliper. Note: When a tumor lesion can be accurately evaluated by both, radiographic imaging and clinical examination, radiographic imaging evaluations should be undertaken.
- Tumor response will be assessed using the modified irRC (Appendix D), at day 1 of week 0, day 1 of week 12 (+1 week) and every 12 weeks (+1 week) thereafter or more frequently if clinically indicated until confirmed PD or start of new anticancer treatment. Response (CR, or PR) or PD occurring after the first dose of pembrolizumab to be confirmed by second consecutive response assessment no less than 4 weeks from the date of the first documented response or PD.
- Talimogene laherparepvec administration
  - day 1 of weeks -5, -2, week 0, and every 2 weeks thereafter until end of study treatment
  - Note: on days when co-administered, talimogene laherparepvec should be administered first, if possible.
- Pembrolizumab administration
  - day 1 of weeks 0, 2, 4, 6, 8, 10, 12 and every 2 weeks thereafter until end of study treatment

Phase 3:

- Vital signs (systolic/diastolic blood pressure, heart rate, respiration rate, temperature): Subject must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position possible. The position selected for a subject should be the same that is used throughout the study and be documented on the vital signs CRF.
  - day 1 of weeks 0, 3, 6, 12 and every 6 weeks until end of study treatment
- Physical examination including body weight, as per standard of care
  - day 1 of week 0
- ECOG performance status
  - day 1 of week 0
- Local laboratory assessments: Screening laboratory values may be used for treatment initiation assessment if completed within 3 days of study treatment initiation. On treatment tests can be performed within 3 days of the planned visit. Results should be reviewed prior to the administration of study treatment.
  - Hematology panel: hemoglobin, hematocrit, WBC with 5-part differential (3-part differential if 5-part unable to be performed), RBC, platelet
    - day 1 of weeks 0, 3, 6, 12 and then every 6 weeks until end of study treatment
  - Chemistry panel: sodium, potassium, chloride, calcium, magnesium, phosphorus, uric acid, total protein, albumin, BUN/urea, creatinine, total bilirubin, alkaline phosphatase, AST, ALT, glucose

  - day 1 of weeks 0, 3, 6, 12 and then every 6 weeks until end of study treatment
- LDH
  - day 1 of weeks 0, 3, 6, 12 and then every 6 weeks until end of study treatment
- Blood sample for total immunoglobulin G (IgG)
  - day 1 of week 0
- Thyroid function tests: T3 (or FT3 per local standard), FT4, TSH
  - day 1 every 6 weeks until end of study treatment
- Urinalysis (blood, glucose, protein, specific gravity) and reflexive microscopic exam only for any abnormal urinalysis result
  - day 1 of weeks 0, 6, 12, 18, 24 and then every 12 weeks until end of study treatment

- Central laboratory assessments:

  - Blood for anti-pembrolizumab antibody (immunogenicity):
    - day 1 of weeks 0, 3, 12, 27, 39 and every 12 weeks (4 cycles) thereafter. Anti-pembrolizumab antibody sample collection and analyses in phase 3 may be discontinued if ongoing antibody results from this study continue to be consistent with existing antibody data from other pembrolizumab melanoma clinical trials.
    - Note: All samples should be drawn within 24 hours before infusion of pembrolizumab and at the same time as the pre-dose trough blood collection for the PK sample.
  - Blood for PK of pembrolizumab:
    - Pre-dose trough and post-dose peak PK samples will be collected at week 0 (ie, pembrolizumab cycle 1). Pre-dose trough PK samples will be collected on day 1 of weeks 3, 12, 27, 39 and every 12 weeks (4 cycles) thereafter. Pembrolizumab PK sample collection and analyses in phase 3 may be discontinued if ongoing PK results from this study continue to be consistent with existing PK data from other pembrolizumab melanoma clinical trials.
    - Note: All trough samples should be drawn within 24 hours before infusion of pembrolizumab. Peak sample should be drawn within 30 minutes after the end of the infusion.

- Tumor response will be assessed using modified irRC-RECIST (Appendix F), at day 1 of week 12 (+1 week) and every 12 weeks (+1 week) thereafter or more frequently if clinically indicated until confirmed iPD or start of new anticancer treatment. Response (iCR, or iPR) or iPD to be confirmed by second consecutive response assessment no less than 4 weeks from the date of the first documented response or iPD. Subjects who have reached a confirmed iCR may increase their interval of radiographic assessments up to 6 months after the first 2 years beyond confirmed iCR and up to 12 months after the first 5 years beyond confirmed iCR as long as iCR is maintained.
  - Radiographic tumor imaging assessments must include CT scan, PET/CT, or MRI of the abdomen, pelvis, and chest and all other sites of disease. In addition, CT scan or MRI of the brain will only be performed if signs or symptoms suggestive of CNS metastasis are present. Imaging will be performed independent of treatment cycle at day 1 of week 0 (phase 1b only), day 1 of week 12 (+1 week), and then every 12 weeks (+1 week) or more frequently if clinically indicated until confirmed iPD per modified irRC-RECIST (Appendix F), or start of new anticancer treatment. Imaging should not be adjusted for cycle initiation delays and performed according to the calendar. The imaging modality selected (eg, CT or MRI) should remain constant for any individual subject.
  - Photographs of visible cutaneous and subcutaneous:
    - Photographs of all visible (ie, visible protrusion from skin surface) cutaneous and subcutaneous tumor lesions not detectable on radiographic imaging must be performed at screening within 28 days prior to enrollment for the purposes of documentation of baseline lesion data. It is critical that baseline photography is captured for subjects with visible cutaneous and subcutaneous tumor lesions in order to allow for follow up of these lesions during the treatment phase.
      During treatment, the photographs of all visible cutaneous and subcutaneous tumor lesions not detectable on radiographic imaging, including new visible cutaneous and subcutaneous lesions, if present, must be performed independent of treatment cycle at day 1 of week 12 (+1 week) and every 12 weeks (+1 week) thereafter or more frequently if clinically indicated until confirmed iPD per modified irRC-RECIST (Appendix F) or start of new anticancer treatment. Photographs must also be taken for previously visible cutaneous and subcutaneous tumor lesions that have resolved at subsequent tumor assessment visits. The schedule of photograph of tumor lesions should not be adjusted for cycle initiation delays and performed according to the calendar. Response or progression should be confirmed by repeated photographs ≥ 4 weeks after the first indication of response or progression.
      Photographs of all visible cutaneous and subcutaneous tumor lesions not detectable on radiographic imaging, including new visible cutaneous and subcutaneous lesions, if present, is required at the safety follow-up visit if the subject ended treatment prior to confirmed iPD and has not had photographs performed within 4 weeks (+1 week) of the visit. For subjects who discontinued treatment for any reason other than iPD, every effort should be made to complete photographs of all visible cutaneous and subcutaneous lesions not detectable on radiographic imaging, including new visible cutaneous and subcutaneous lesions, if present, every 12 weeks (+1 week) or more frequently if clinically indicated during the long-term follow-up until documentation of confirmed iPD per modified irRC-RECIST (Appendix F), start of new anticancer treatment, or end of study, whichever occurs first.

- The photographic images will be collected for review of tumor response by a blinded independent central review committee. Photographed lesions not appearing on radiographic imaging should only be considered non-target lesions.

  Note: When a lesion can be accurately evaluated by both radiographic imaging and photographs, radiographic imaging evaluations must be undertaken. When a lesion/lesions can not be evaluated by radiographic imaging, but can be accurately evaluated by both clinical examination and photographs, photographs must be undertaken.
- Photographs must also be taken for previously visible cutaneous and subcutaneous tumor lesions that have resolved at subsequent tumor assessment visits.

- Completion of PRO (EQ-5D-3L and QLQ-C30) questionnaires (PRO questionnaires will be administered to subjects where translations are available):
  - prior to study treatment administration at day 1 of weeks 0, 3, 6, 9, 12, then every 6 weeks until end of study treatment.
  - For subjects with progressive disease, QLQ-C30 will no longer be collected, and EQ-5D-3L will be collected through the long-term follow-up.
- Talimogene laherparepvec or placebo administration
  - day 1 of weeks 0, 3, 5, 7, 9, and every 3 weeks thereafter until end of study treatment
  - Note: on days when co-administered, talimogene laherparepvec should be administered first, if possible.
- Pembrolizumab administration
  - day 1 of weeks 0, 3, 6, 9, and every 3 weeks thereafter until end of study treatment

7.2.3 Safety Follow-up 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. If an end of treatment decision occurs > 30 (+7) days after the last treatment date, then the safety follow-up should be performed as soon as possible (eg, within a week of the end of treatment decision). Applicable safety follow-up procedures should occur even if the subject has initated new anticancer therapy.

<u>Phase 1b and 3:</u>

- Vital signs (systolic/diastolic blood pressure, heart rate, respiration rate, temperature): Subject must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position possible. The position selected for a subject should be the same that is used throughout the study and be documented on the vital sign CRF.

- Physical examination including body weight as per standard of care
- ECOG performance status assessment
- A 12-lead ECG. The ECG must include the following measurements: heart rate, PR, QRS, QT and QTc intervals.
- Local laboratory Assessments: Tests can be performed within 3 days of the planned visit.
  - hematology panel: hemoglobin, hematocrit, WBC count with 5-part differential (3-part differential if 5-part unable to be performed), RBC count, platelets
  - chemistry panel: sodium, potassium, chloride, calcium, magnesium, phosphorus, uric acid, total protein, albumin, BUN (phase 1b only), BUN/urea (phase 3), creatinine, total bilirubin, alkaline phosphatase, AST, ALT, glucose
  - LDH test (phase 3 only)
  - thyroid function tests: T3 (or FT3 per local standard), FT4, TSH
  - serum or urine pregnancy test for female subjects of childbearing potential
  - urinalysis (blood, glucose, protein, specific gravity) and reflexive microscopic exam only for any abnormal urinalysis results
- Central laboratory assessments:

  [redacted]

  - Swab of cold sore, vesicles and other lesions suspected to be herpetic in origin (if any) for qPCR testing of talimogene laherparepvec DNA:
    - Upon notification of a suspected herpetic lesion by the subject, the subject should return to the clinic within 3 days of the occurrence of a reportable lesion suspected to be herpetic in origin. The lesion should be evaluated by the investigator and swabbed if HSV infection is suspected. A qPCR analysis will be performed on the swab sample to evaluate whether the talimogene laherparepvec DNA is detectable in the sample.
  - Blood for anti-pembrolizumab antibody (immunogenicity). Anti-pembrolizumab antibody sample collection and analyses in phase 3 may be discontinued if ongoing antibody results from this study continue to be consistent with existing antibody data from other pembrolizumab melanoma clinical trials.
  - Blood for PK pembrolizumab: sample taken at the same time as blood sample for anti-pembrolizumab antibody. Pembrolizumab PK sample collection and analyses in phase 3 may be discontinued if ongoing PK results from this study continue to be consistent with existing PK data from other pembrolizumab melanoma clinical trials.
- Recording of adverse events
- Recording of serious adverse events: Serious adverse events that occur within 90 (+7) days after the cessation of all study treatment or 30 (+7) days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, will be reported within 24 hours following the investigator's knowledge of the event.

- For subjects treated with pembrolizumab: Selected non-serious and serious adverse events known as pembrolizumab Events of Clinical Interest (ECI) must be reported to Amgen within 24 hours of the investigator's knowledge of the event regardless of attribution to pembrolizumab (see Section 9.5).
- Documentation of concomitant medications
- Completion of PRO (EQ-5D-3L and QLQ-C30) questionnaires

Phase 1b:

- Radiographic tumor imaging, clinical tumor assessment, photographic assessment, and tumor response assessments are to be performed if the subject ended study treatment prior to confirmed PD per modified irRC (Appendix D) and has not had assessments performed within 4 weeks (+1 week) of the visit.
  - Radiographic tumor imaging assessments must include CT scan, PET/CT, or MRI of the abdomen, pelvis, and chest along with all other sites of disease. In addition, CT scan or MRI of the brain will only be performed if signs or symptoms suggestive of CNS metastasis are present.
  - Photographic imaging assessments of visible cutaneous and subcutaneous lesions:
    - Photographs of visible cutaneous and subcutaneous index tumor lesions and of new visible lesion cutaneous and subcutaneous, if present.
    - Note: When a tumor lesion can be accurately evaluated by both, radiographic imaging and photographs, radiographic imaging evaluations should be undertaken.
  - Clinical tumor assessments must include clinical measurement of cutaneous, subcutaneous, or palpable nodal tumor lesions by caliper. Note: When a tumor lesion can be accurately evaluated by both, radiographic imaging and clinical examination, radiographic imaging evaluations should be undertaken.
  - Tumor response will be assessed using the modified irRC. Response (CR or PR) or PD to be confirmed by second consecutive response assessment no less than 4 weeks from the date of the first documented response or PD.

Phase 3:

- Radiographic tumor imaging, clinical tumor assessment, photographic assessment, and tumor response assessments are to be performed if the subject ended study treatment prior to confirmed iPD per modified irRC-RECIST (Appendix F) and has not had assessments performed within 4 weeks (+1 week) of the visit.
  - Radiographic tumor imaging assessments must include CT scan, PET/CT, or MRI of the abdomen, pelvis, and chest along with all other sites of disease. In addition, CT scan or MRI of the brain will only be performed if signs or symptoms suggestive of CNS metastasis are present.
  - Photographic imaging assessments of visible cutaneous and subcutaneous lesions:
    - Photographs of all visible (ie, visible protrusion from skin surface) cutaneous and subcutaneous tumor lesions not detectable on radiographic imaging must be performed.

- Note: When a tumor lesion can be accurately evaluated by both, radiographic imaging and photographs, radiographic imaging evaluations must be undertaken. When a lesion/lesions can not be evaluated by radiographic imaging, but can be accurately evaluated by both clinical examination and photographs, photographs must be undertaken. Photographs must also be taken for previously visible cutaneous and subcutaneous tumor lesions that have resolved at subsequent tumor assessment visits.

– Tumor response will be assessed using modified irRC-RECIST (Appendix F). Response (CR or PR) or iPD to be confirmed by second consecutive response assessment no less than 4 weeks from the date of the first documented response or iPD.

The Safety Follow-up visit is not required for those subjects who are randomized, but do not receive any doses of investigational product.

7.2.4 Long-term Follow-up

All subjects who permanently discontinue study drug for any reason other than withdraw of full consent will be contacted by clinic visit or telephone to assess survival, initiation of additional melanoma therapy, and whether any injected investigational product-related adverse events has occurred.

Contact for all subjects will be attempted every 12 weeks (± 28 days) following the safety follow-up visit until death, subject withdraws full consent, or up to 60 months after the end of randomization of phase 3. The sponsor may request survival status to be assessed at additional time points during the course of the study.

For subjects discontinuing study treatment without a documented confirmed PD, clinical tumor assessment (phase 1b only), radiographic imaging, photographic imaging, and tumor response assessment as detailed in Section 7.2.2 and PRO (EQ-5D-3L and QLQ-C30) questionnaires will be performed every 12 weeks (+1 week) or more frequently if clinically indicated until documented confirmed PD per modified irRC in phase 1b (Appendix D) or iPD per modified irRC-RECIST in phase 3 (Appendix F), start of new anticancer treatment, death, or end of study, whichever occurs first. For subjects with progressive disease, QLQ-C30 will no longer be collected, and EQ-5D-3L will be collected through the long-term follow-up. Subjects who have reached a confirmed CR may increase their interval of radiographic assessments up to 6 months after the first 2 years beyond confirmed CR and up to 12 months after the first 5 years beyond confirmed CR as long as CR is maintained.

Blood for anti-pembrolizumab antibody and blood for PK of pembrolizumab will be collected at 3 and 6 months after study discontinuation or up until the subject starts new anticancer therapy, whichever occurs first. Anti-pembrolizumab antibody and pembrolizumab PK sample collection and analyses in phase 3 may be discontinued if ongoing antibody and PK results from this study continue to be consistent with existing antibody and PK data from other pembrolizumab melanoma clinical trials.

All subjects treated with talimogene laherparepvec (all phase 1b subjects and those who received talimogene laherparepvec in phase 3) and who permanently discontinue study will be eligible to continue follow-up for survival under an ongoing separate registry protocol that is in place for the long-term follow-up of subjects treated with talimogene laherparepvec in clinical trials. The registry protocol, including for phase 1b subjects, will not apply until the end of the study or 5 years after the last subject is enrolled in phase 3, whichever comes first. The registry protocol will also monitor for late and long-term adverse events thought to be potentially related to talimogene laherparepvec.

7.2.5 Reporting Unintended Exposure to Talimogene Laherparepvec in Phase 1b and Phase 3

If a household member, caregiver, or healthcare provider who has had close contact with the subject is suspected to have been exposed to talimogene laherparepvec (eg, has or who has had signs or symptoms suspected to be herpetic in origin or accidentally exposed to talimogene laherparepvec), report the potential or known unintended exposure to talimogene laherparepvec, suspected related signs or symptoms, and detection of talimogene laherparepvec in a subject's household member, caregiver, or healthcare provider as specified Section 9.4.

[redacted]

7.3.1 Blood Samples

Blood samples are to be collected for [redacted] development as described in Sections 7.2.2 and 7.2.3.

7.3.2 Archived Tumor Tissue Sample

A block of formalin-fixed paraffin-embedded tumor tissue collected prior to the study is to be sent to the central laboratory along with the corresponding pathology report (if available) as described in Section 7.2.1. The tumor block is to be carefully selected by a pathologist or a skilled experienced histology associate to include generous tumor tissue using the Pathology Report as a guide. In lieu of a block, approximately 20 unstained sections on charged slides from the same block can be submitted. When the samples of tumor tissues are available, analyses of tumor specific mutations or epigenetic changes may be performed (eg, somatic mutations).

[redacted]

7.4 Pharmacogenetic Studies

If the subject consents to the optional pharmacogenetic portion of this study, DNA analyses may be performed. These optional pharmacogenetic analyses focus on inherited genetic variations to evaluate their possible correlation to the disease and/or responsiveness to the therapies used in this study. The goals of the optional studies include the use of genetic markers to help in the investigation of cancer and/or to identify subjects who may have positive or negative responses to talimogene laherparepvec and/or pembrolizumab. No additional samples are collected for this part of the study. For subjects who consent to this/these analysis/analyses, DNA may be extracted.

7.5 Sample Storage and Destruction

Any blood, tumor, or swab samples collected according to the Schedule of Assessments (Table 5 and Table 6) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be coded prior to being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the study. Results are stored in a secure database to ensure confidentiality.

If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the cancer, the dose response and/or prediction of response to talimogene laherparepvec and/or pembrolizumab, characterize antibody response, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from these analyses are to be documented and maintained, but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

Since the qPCR testing of talimogene laherparepvec DNA from swabs of cold sores, vesicles, and other lesions suspected to be herpetic in origin are not expected to be available in time to benefit the subject directly or to alter the treatment course, the results of qPCR testing will not be provided unless requested by the investigator or the subject. Results may not be available until the end of the study. The evaluations of pharmacogenetic, [redacted] or other exploratory studies are not expected to benefit the subject directly or to alter the treatment course. The results of pharmacogenetic, [redacted] or other exploratory studies are not placed in the subject's medical record and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The subject retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the subject, the investigator is to provide the sponsor with the required study and subject number so that any remaining blood and tumor samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples prior to the request for destruction, will be retained by Amgen.

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this

research project, the sponsor owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample.
See Section 11.3 for subject confidentiality.

7.6 Patient Reported Outcomes

PROs will be assessed using the following questionnaires: the EQ-5D-3L and QLQ-C30. The two questionnaires are commonly used, uniformly accepted and validated instruments to evaluate health outcomes in subjects with cancer. PRO questionnaires will be administered to subjects where translations are available. PRO questionnaires will be collected via pen and paper. During long term follow-up for subjects who have progressed, EQ-5D-3L may be collected via the telephone.

7.6.1 EORTC QLQ-C30

The EORTC QLQ-C30 Version 3 is a 2-page, self-reporting 30-item generic instrument for use in cancer subjects across tumor types (Bjordal et al, 2000). It assesses 15 domains consisting of 5 functional domains (physical, role, emotional, cognitive, social), 9 symptom domains (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties), and a Global Health Status-Quality of Life (GHS-QOL) subscale (Aaronson et al, 1993).

7.7 Health State Utility Estimates

Health state utility estimates for the purpose of inclusion in a health economic model will be derived using the EQ-5D-3L.

7.7.1 EQ-5D-3L

The EQ-5D-3L questionnaire is a 2-page, generic preference-based QoL measure comprised of a 5-item health status measure and a visual analogue scale (VAS) (Rabin and de Charro, 2001; Kind, 1996) and is used to generate 2 scores. The EQ-5D-3L utility score is based on answers to 5 questions that evaluate mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D-3L VAS generates a single health status index and the analogue scale ranges from 0 to 100 in which subjects are asked to rate their current health state by drawing a line from a box marked, "Your health today."

8. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

8.1 Subjects' Decision to Withdraw

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product or other protocol-required therapies and must discuss with the subject the options for continuation of the Schedule of Assessments (Table 5 and Table 6) including different options for follow-up (eg, in person, by phone/email, through family/friends, in correspondence/communication with other treating physicians, the review of medical records) and collection of data, including endpoints and adverse events. Subjects that have discontinued investigational product and/or protocol required therapies or procedures should not be automatically removed from the study. Whenever safe and feasible, it is imperative that subjects remain on study to undergo safety surveillance and/or collection of outcome data. The investigator must document the change to the Schedule of Assessments (Table 5 and Table 6) and the level of follow-up that is agreed to by the subject (eg, in person, by telephone/mail, through family/friends, in correspondence/communication with other physicians, from review of the medical records).

For subjects who discontinue investigational product without documented PD and have not initiated a new anticancer therapy, every effort should be made to continue monitoring tumor response status by clinical and radiographic tumor assessments, and to complete PRO questionnaires as described in Table 6.

Those subjects who discontinue investigational product should continue into the long-term follow-up. Subjects will be followed for survival and subsequent anticancer therapies every 12 weeks (± 28 days) for approximately 60 months after the last subject is enrolled in phase 3. In addition, talimogene laherparepvec- or placebo-related adverse events that occur through the end of the long-term follow-up will be reported.

For those subjects who are randomized but do not receive any doses of investigational product, every effort should be made to continue monitoring tumor response status by clinical and radiographic tumor assessments as described in Table 6. They should continue into the long-term follow-up and be followed for survival and subsequent

anticancer therapies every 12 weeks (± 28 days) for approximately 60 months after the last subject is enrolled in phase 3.

Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publicly available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

8.2 Investigator or Sponsor Decision to Withdraw or Terminate Subjects' Participation Prior to Study Completion

The investigator and/or sponsor can decide to withdraw a subject from investigational products and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion.

Subjects may be eligible for continued treatment with Amgen investigational product and/or other protocol-required therapies by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with Section 12.1.

8.3 Reasons for Removal From Treatment, or Study

8.3.1 Reasons for Removal From Treatment

Reasons for removal from protocol-required investigational products or procedural assessments include any of the following:

- completed study treatment
  - Phase 1b and phase 3: completed 24 months of treatment with talimogene laherparepvec/placebo and/or pembrolizumab. Note: For phase 1b, 24 months of study treatment is calculated from the date of first dose of pembrolizumab.
- subject request
- safety concern (eg, due to an adverse event)
- ineligibility determined
- protocol deviation
- non-compliance
- requirement for alternative therapy
- pregnancy
- death
- lost to follow-up
- decision by sponsor (other than subject request, safety concern, lost to follow-up)

- decision by investigator (other than subject request, safety concern, lost to follow-up)
- confirmed PD per modified irRC in phase 1b (Appendix D) or iPD per modified irRC-RECIST (Appendix F)
  - Note: A subject may be granted an exception to end treatment for nonconfirmed PD if deterioration of health status requires discontinuation of treatment (see Section 3.1.3.1 and Appendix D for phase 1b or Section 3.1.3.3 and Appendix F for phase 3).
- other protocol-specified criteria (see Sections 6.2.1.2, 6.2.2.2, and 6.2.2.3).
- subject's treatment assignment is unblinded during the double-blind phase of the study via IVRS for the future management of the subject, and subject is not allowed to continue treatment (see Section 5.2)

8.3.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- decision by sponsor
- full withdrawal of consent from study
- death
- lost to follow-up

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Definition of Safety Events

9.1.1 Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment. The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject are recorded in the subject's medical record.

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition or underlying disease (eg, diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration more than what would be expected, and/or has an association with a significantly worse outcome than expected. A pre-existing condition that has not worsened more than anticipated (ie, more than usual fluctuation of disease) during the study or involves an intervention such as elective cosmetic surgery or a medical procedure while on study, is not considered an adverse event.

For situations when an adverse event or serious adverse event is due to melanoma, report all known signs and symptoms. Death due to disease progression in the absence of signs and symptoms should be reported as the primary tumor type (eg, melanoma).

Note: The term “disease progression” should not be used to describe the adverse event.

The investigator’s clinical judgment is used to determine whether a subject is to be removed from treatment due to an adverse event. In the event a subject, or subject’s legally acceptable representative requests to withdraw from protocol-required therapies or the study due to an adverse event, refer to Section 8.1 for additional instructions on the procedures recommended for safe withdrawal from protocol-required therapies or the study.

9.1.2 Serious Adverse Events

A serious adverse event is defined as an adverse event that meets at least 1 of the following serious criteria:

- fatal
- life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- congenital anomaly/birth defect
- other medically important serious event

An adverse event would meet the criterion of “requires hospitalization”, if the event necessitated an admission to a health care facility (eg, overnight stay).

If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as a serious adverse event under the criterion of “other medically important serious event”. Examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

9.2 Safety Event Reporting Procedures

9.2.1 Adverse Events

9.2.1.1 Reporting Procedures for Adverse Events That do not Meet Serious Criteria

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after first dose of talimogene laherparepvec/placebo or pembrolizumab through the safety follow-up visit (ie, 30 [+7] days after the last dose of talimogene laherparepvec/placebo or pembrolizumab, whichever is later, are reported using the applicable CRF (eg, Adverse Event Summary). In addition, injected investigational product-related adverse events that occur during the long term safety follow-up period until the end of study should also

be captured in the Adverse Event CRF although these events will not be considered treatment-emergent adverse events.

The investigator must assign the following adverse event attributes:

- Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms),
- Dates of onset and resolution (if resolved),
- Severity [and/or toxicity per protocol],
- Assessment of relatedness to injected investigational product and/or pembrolizumab, and
- Action taken.

The adverse event grading scale used will be the CTCAE version 4.0. The grading scale used in this study is described in Appendix A. The investigator must assess whether the adverse event is possibly related to injected investigational product and/or pembrolizumab. This relationship is indicated by a "yes" or "no" response to the question: Is there a reasonable possibility that the event may have been caused by injected investigational product and/or pembrolizumab?

The investigator must assess whether the adverse event is possibly related to any study-mandated activity and/or procedure (including any screening procedures). This relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by a study activity and/or procedure"?

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

If the severity of an adverse event worsens from the date of onset to the date of resolution, record a single event for each increased level of severity on the Adverse Event Summary CRF. The investigator is expected to follow reported adverse events until stabilization or reversibility.

9.2.1.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through 90 (+7) days after the cessation of all study treatment or 30 (+7) days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, are recorded in the subject's medical record and are submitted to Amgen. All serious adverse events must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the applicable CRF.

After the protocol-required reporting period defined above, the investigator does not need to actively monitor subjects for serious adverse events. However, if the investigator becomes aware of a serious adverse event after this protocol-required reporting period, the investigator will report the event to Amgen within 24 hours following the investigator's knowledge of the event. Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases for the purposes of expedited reporting.

If the electronic data capture (EDC) system is unavailable to the site staff to report the serious adverse event, the information is to be reported to Amgen via an electronic serious adverse event (eSAE) Contingency Report Form within 24 hours of the investigator's knowledge of the event. See Appendix B for a sample of the Serious Adverse Event Worksheet /electronic Serious Adverse Event Contingency Report Form. For EDC studies where the first notification of a Serious Adverse Event is reported to Amgen via the eSAE Contingency Report Form, the data must be entered into the EDC system when the system is again available.

The investigator must assess whether the serious adverse event is possibly related to injected investigational product and/or pembrolizumab. This relationship is indicated by a "yes" or "no" response to the question: Is there a reasonable possibility that the event may have been caused by the injected investigational product and/or pembrolizumab?

The investigator must assess whether the serious adverse event is possibly related to any study-mandated activity or procedure. This relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by a study activity/procedure"? Relatedness means that there are facts or reasons to support a relationship between investigational product and the event.

The investigator is expected to follow reported serious adverse events until stabilization or reversibility.

New information relating to a previously reported serious adverse event must be submitted to Amgen. All new information for serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. The investigator may be asked to provide additional follow-up information, which may include a discharge summary or extracts from the medical record. Information provided about the serious adverse event must be consistent with that recorded on the applicable CRF (eg, Adverse Event Summary CRF).

If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.

To comply with worldwide reporting regulations for serious adverse events, the treatment assignment of subjects who develop serious, unexpected, and related adverse events may be unblinded by Amgen before submission to regulatory authorities. Investigators will receive notification of related serious adverse events reports sent to regulatory authorities in accordance with local requirements.

Amgen will report serious adverse events and/or suspected unexpected serious adverse reactions as required to regulatory authorities, investigators/institutions, and IRBs/IECs in compliance with all reporting requirements according to local regulations and good clinical practice.

The investigator is to notify the appropriate IRB/IEC of serious adverse events occurring at the site and other reports received from Amgen, in accordance with local procedures and statutes.

9.3 Pregnancy and Lactation Reporting

If a female subject becomes pregnant, or a male subject fathers a child, while the subject is taking protocol-required therapies report the pregnancy to Amgen Global Patient Safety as specified below.

In addition to reporting any pregnancies occurring during the study, investigators should report pregnancies that occur through 3 months after the last dose of talimogene laherparepvec or 4 months after the last dose of pembrolizumab (or 30 days following cessation of pembrolizumab if the subject initiates a new anticancer therapy, whichever is earlier).

The pregnancy should be reported to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C). Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

If a female subject becomes pregnant during the study, the investigator should attempt to obtain information regarding the birth outcome and health of the infant.

If the outcome of the pregnancy meets a criterion for immediate classification as a Serious Adverse Event (eg, female subject experiences a spontaneous abortion, stillbirth, neonatal death, or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a Serious Adverse Event.

If a female breastfeeds while taking protocol-required therapies report the lactation case to Amgen as specified below.

In addition to reporting a lactation case during the study, investigators should monitor for lactation cases that occur after the last dose of protocol-required therapies through 3 months after the last dose of talimogene laherparepvec or 4 months after the last dose of pembrolizumab (or 30 days following cessation of pembrolizumab if the subject initiates a new anticancer therapy, whichever is earlier).

Any lactation case should be reported to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event. Report a lactation case on the Lactation Notification Worksheet (Appendix C). Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

If a male subject's female partner becomes pregnant, the investigator should discuss obtaining information regarding the birth outcome and health of the infant from the pregnant partner.

9.4 Reporting of Unintended Exposure to Talimogene Laherparepvec or Placebo

If a household member, caregiver, or healthcare provider who has had close contact with a subject treated with talimogene laherparepvec or placebo on this study is suspected to have been exposed to talimogene laherparepvec or placebo (eg, have or who have had signs or symptoms suspected to be herpetic in origin or who have been accidentally exposed to talimogene laherparepvec or placebo), while the subject is taking talimogene laherparepvec or placebo, report the exposure to Amgen as specified below. In addition to reporting an unintended exposure case during the study treatment,

investigators should monitor for potential exposure cases that occur after the last dose of talimogene laherparepvec or placebo through 30 (+7) days after the last dose of talimogene laherparepvec or placebo.

Any potential or known unintended exposure should be reported to Amgen within 24 hours of the investigator's knowledge of the event of exposure. Amgen will seek to follow up with the exposed individual, if necessary, to collect more information about the exposed individual contact with clinical trial subject, signs and/or symptoms related to the exposure, medical history, and/or outcome of the exposure. If the exposed individual is reporting sign or symptoms suspected to be related to talimogene laherparepvec or placebo exposure, the exposed individual may be asked to have a swab taken to evaluate for the presence of talimogene laherparepvec DNA in the lesion.

9.5 Pembrolizumab Events of Clinical Interest (ECI)

Selected non-serious and serious adverse events known as Pembrolizumab ECI must be reported to Amgen within 24 hours.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow-up to an ECI, that occurs to any subject must be reported within 24 hours to Amgen 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 30 days following cessation of treatment, any ECI, or follow-up to an ECI, whether or not related to pembrolizumab, must be reported within 24 hours to Amgen.

Pembrolizumab Events of Clinical Interest for this trial include:

- an overdose of pembrolizumab, as defined in Section 9.6
- 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.

9.6 Definition of an Overdose of Pembrolizumab for This Protocol and Reporting of Pembrolizumab Overdose

For the purpose of this trial, an overdose of pembrolizumab will be defined as > 1000 mg (5 times the dose of pembrolizumab). No specific information is available on the treatment of overdose of pembrolizumab. 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) or serious adverse event(s) is associated with ("result from") the overdose of pembrolizumab, the adverse event(s) or serious adverse event is to be reported to Amgen as described in Sections 9.2.1.1 and 9.2.1.2, respectively. In addition, the adverse event(s) or serious adverse event(s) associated with ("result from") the overdose of pembrolizumab should be reported as Event of Clinical Interest as described in Section 9.5.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

10.1.1.1 Primary Endpoints

Phase 1b:

- Incidence of DLT

Phase 3:

- Progression-free Survival by blinded independent central review using modified RECIST (PFS): Time from randomization to the date of disease progression (response evaluation by blinded independent central review using modified RECIST 1.1) or death, whichever occurs earlier.
- Overall Survival (OS): Time from randomization date to the date of death from any cause.

10.1.1.2 Secondary Endpoints

Phase 1b:

- Confirmed ORR (CR+PR) (response evaluation by investigator using modified irRC).
- BOR, DRR (duration of response for 6 months or longer), DOR (the time from date of the initial confirmed response to the date of the first documented PD or death), DCR, and PFS (response evaluation by investigator using modified irRC).
- OS.
- Incidence of treatment-emergent and treatment-related adverse events (all AEs, grade ≥ 3 AEs, SAEs, fatal AEs, AEs defined as events of interest), and abnormal laboratory tests.

Phase 3:

- iCRR by blinded independent central review using modified irRC-RECIST
- iPFS by blinded independent central review using modified irRC-RECIST
- OS in subjects excluding stage IVM1c per CRF
- ORR (CR + PR), BOR, DRR, DOR (the time from date of the initial confirmed response to the date of the first documented PD or death), and DCR (response evaluation by blinded independent central review using modified RECIST 1.1), and iORR (iCR + iPR), iBOR, iDRR, iDOR, and iDCR response evaluation by blinded independent central review using modified irRC-RECIST).
- Incidence of treatment-emergent and treatment-related adverse events (all AEs, grade ≥ 3 AEs, SAEs, fatal AEs, and AEs defined as events of interest), and abnormal laboratory tests.
- Changes in EORTC QLQ-C30 GHS/QoL subscale.

10.1.1.3 Exploratory Endpoints

[redacted]

- iORR (iCR + iPR), iBOR, iDRR, iDOR, and iPFS (response evaluation by investigator using modified irRC-RECIST).

[redacted]

- Changes in the EORTC QLQ-C30 subscales.
- **Changes in** HSU estimates derived via EQ-5D-3L.

[redacted]

- Incidence of anti-pembrolizumab antibodies.
- Descriptive statistics of trough and peak levels of pembrolizumab (MK-3475).

[redacted]

10.1.2 Analysis Sets

DLT Analysis Set

The DLT analysis set will include DLT-evaluable subjects enrolled in phase 1b who have had the opportunity to be on treatment for at least 6 weeks from the initial dosing of

pembrolizumab and received at least 2 doses of talimogene laherparepvec and 2 doses of pembrolizumab in combination (ie, on the same day) or otherwise experienced a DLT within 6 weeks after starting the combination therapy.

Full Analysis Set

The primary analysis of all efficacy endpoints for phase 3 part of the study, unless noted otherwise, will be conducted on the full analysis set defined as all randomized subjects. All subjects will be analyzed according to treatment to which they are randomized.

Safety Analysis Set

The safety analysis set will include all subjects who received at least 1 dose of talimogene laherparepvec or pembrolizumab. The safety analysis set will be defined separately for the phase 1b and phase 3. For phase 3 all subjects will be analyzed according to the treatment they received.

[redacted]

PRO **Population**

The PRO population includes the subset of the subjects in the full analysis set who had received at least 1 dose of study therapy and had at least 1 PRO assessment. A PRO assessment will be defined as completed if at least 1 subscale/domain can be calculated from the questionnaire. Patient reported outcome populations will be defined separately for each questionnaire (EORTC QLQ-C30 and EQ-5D-3L) and for the secondary endpoint of EORTC QLQ-C30 GHS/QoL.

10.1.3 Covariates and Subgroups

Randomization will be stratified by stage of disease: less advanced stages (IIIB, IIIC, and IVM1a) versus more advanced stages (IVM1b and IVM1c) and by prior BRAF inhibitor therapy: no prior BRAF inhibitor versus prior BRAF inhibitor with or without MEK inhibitor.

The following baseline covariates and randomization stratification factors may be used to examine efficacy in subgroups or in multivariate analyses:

- Region, if applicable (USA or non-USA)
- Age: < 50, ≥ 50; < 65, ≥ 65; < 75, ≥ 75 years
- Individual disease stage: IIIB vs IIIC vs IVM1a vs IVM1b vs IVM1c
- Grouped disease stage: IIIB/C-IVM1a vs IVM1b/c (CRF and IVRS)
- Grouped disease stage: IIIB/C-IVM1b vs IVM1c
- LDH: ≤ ULN vs > ULN
- Sex (female vs male)
- ECOG performance status (0 vs 1)
- HSV-1 serostatus (positive vs negative)
- The sum of longest, or shortest for nodal, diameters of target lesions (SLD) **determined by blinded independent central review (will be dichotomized based on median)**
- **Baseline** PD-L1 status (positive **vs not positive**)
- Prior BRAF inhibitor (none vs BRAF inhibitor alone vs BRAF and MEK inhibitors in combination): if subjects included in each of the 2 BRAF related category represent ≥ 10% of the study population (CRF)
- Prior BRAF inhibitor (yes versus no BRAF inhibitor with or without MEK inhibitors) (IVRS)
- **Baseline** of $BRAF^{V600}$ mutation: yes vs no **vs missing/unknown**

10.2 Sample Size Considerations

10.2.1 Sample Size Considerations for Phase 1b

Six to nine DLT-evaluable subjects will be required to assess the DLT profile of talimogene laherparepvec in combination with pembrolizumab for phase 1b. The sample size of approximately 6 to 9 subjects is determined empirically and is consistent with those used in 6+3 phase 1 designs to evaluate the safety of a single dose of each agent assuming a true incidence rate of DLT is 11 to 33%. Additional subjects, up to a total of 20, will be enrolled in the phase 1b portion of the trial to address the secondary objective exploring the relationship between [redacted] and response to treatment.

[redacted]

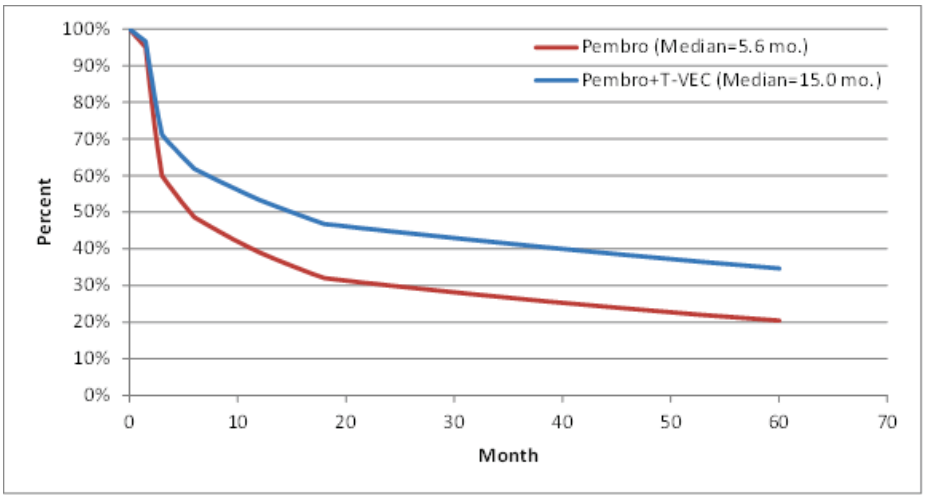
[redacted]

[redacted]

10.2.2 Sample Size Considerations for Phase 3

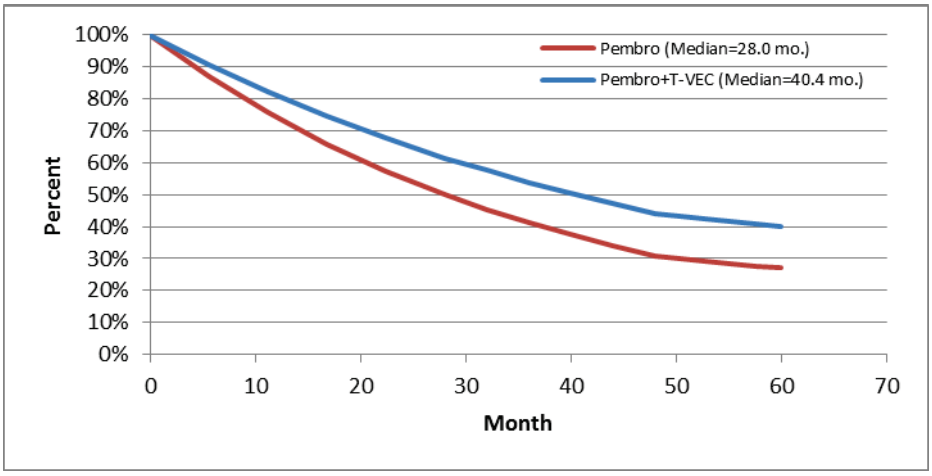
There are 2 primary endpoints for phase 3, PFS and OS. A 1/3 reduction in hazard ratio (talimogene laherparepvec with pembrolizumab / placebo with pembrolizumab) for PFS (HR = 0.67), and a hazard ratio of 0.70 for OS are hypothesized in the Full Analysis Set. Assuming events follow piece-wise exponential distributions (Figure 1 and Figure 2), the hypothesized HRs will translate into a relative increase of 167% in median PFS time and 44% in median OS time. The absolute increase in median PFS will be 9.4 months (5.6 to 15.0 months) in the talimogene laherparepvec and placebo arm and 12.4 months (28 to 40.4 months) in median OS.

Figure 1. Progression-free Survival



Median PFS (pembrolizumab), 5.6 months; p(t) = event rate at month t; p(1.5) = 0.95; p(3) = 0.6; p(6) = 0.49; p(12) = 0.39; p(18) = 0.32; p(24) = 0.30; constant hazard in each interval between 2 consecutive pieces; a constant hazard ratio across all pieces.

Figure 2. Overall Survival



Median OS (pembrolizumab) = 28 months; p(t) = event rate at month t; p(48) = 0.31 and p(60) = 0.27; constant hazard in each interval between 2 consecutive pieces; a constant hazard ratio across all pieces.

The overall Type I error for the dual primary endpoints is 2-sided 0.05. The event goal for PFS to achieve 90% power at 2-sided 0.005 is 407 and that for OS to achieve 90% power at a 2-sided 0.045 is 346 after taking into account the group-sequential interim OS analyses. The OS event goal is not adjusted for the non-binding OS futility assessment at the second OS interim analysis. The sample size is 660 (ie, 330 per arm) based on an estimate of 346 death events occurring within 5 years (60 months) with approximately 48% of subjects censored. Assuming a non-uniform subject accrual rate for which 50% of cumulative enrollment is accrued at 2/3 of expected total enrollment period (Lachin and Foulkes, 1986), and exponential distributions for loss to follow up for PFS and OS with an annual rate of 5% for OS and 10% for PFS, Table 9 displays estimated timing of analysis based on **the actual** enrollment rate:

Table 9. Timing of Primary Analysis for PFS (at 407 events) and OS (at 346 events)

	Enrollment Duration (month)	PFS PA DCO (month)	OS Events (% event goal) at PFS PA DCO	OS PA DCO (month)
	26	**48**	**252** (**73**%)	**75**

DCO = data cutoff at event goal; OS = overall survival; PA = primary analysis; PFS_1 = progression free survival per blinded independent central review using modified RECIST 1.1.

[redacted]. **Timings are further informed by event projection simulations based on KEYNOTE-006 year 4 data for all subjects in the pembrolizumab arm. Analysis timings assume the hypothesized constant hazard ratio of 0.67 for PFS and 0.70 for OS (see Table 10 below).**

In addition to hypothesis tests for the dual primary endpoints, statistical tests of the secondary endpoints, iCRR and iPFS, by blinded independent central review using

modified irRC-RECIST, and OS in the disease subgroup excluding IVM1c, will be performed. Table 10 shows event goals (or analysis time) based on hypothesized effect sizes and simulated powers for testing 5 endpoints, where PFS and iPFS refer to the modified RECIST 1.1 and modified irRC-RECIST criterion, respectively. The simulated powers are based on the Maurer-Bretz graphic-based multiple testing procedure (Maurer and Bretz, 2013) assuming a 1-time analysis. Details of the multiple testing procedure are described in Section 10.5.

Table 10. Hypothesized Effect Sizes and Hypothesis Test Powers

Hypothesis	Effect Size	Primary Analysis Timing	Simulated Power[a]
H_1 (OS)	HR = 0.70	346 events	91%
H_2 (PFS)	HR = 0.67	407 events	90%
H_3 (iPFS)	HR = 0.60	256 events	94%
H_4 (iCRR)	OR = 3.9	DCO for PFS PA	97%
H_5 (OS subgroup)	HR = 0.60	Earlier of 208 events or 5 years minimum follow-up	90%

DCO = data cutoff at event goal; H = hypothesis; HR = hazard ratio; iCRR = complete response rate (by modified irRC-RECIST); iPFS = progression free survival (by modified irRC-RECIST); OR = odds ratio; OS = overall survival; PA = primary analysis; PFS = progression free survival

[redacted]

A CRR (95% CI) of 24% (8-47), per modified irRC, was observed in phase 1b subjects of the study with 36 weeks minimum follow-up time (Long et al, 2016). It is also reported that CRR in pembrolizumab, per RECIST, was 5% (3-8) from KEYNOTE-006 (Joseph et al, 2014) and 3% (1-10), per irRC, from KEYNOTE-001 (Robert et al, 2015). Assuming 6% CRR in pembrolizumab and 20% in the combination arm, then the odds ratio of 3.9 is hypothesized for iCRR in the phase 3 part of the study.

10.3 Access to Individual Subject Treatment Assignments by Amgen or Designees

To guard against actual or perceived bias due to subjective decisions made by Amgen or Designee in light of potentially unblinding data captured during phase 3 of the study, the study team will comply with Amgen standard operating procedures that govern restricted and potential unblinding data access. Subject-level unblinding data will be available to an external independent biostatistics group that supports the DMC safety and efficacy reviews. The external DMC will be the primary reviewer of the unblinding results for interim safety, efficacy, and futility analyses prior to the primary analysis of OS (see Section 10.4.3). If the DMC recommends to stop the study due to safety concerns

or declares that an efficacy or futility criterion has been met, then the sponsor may unblind a restricted study team as deemed necessary.

Unblinding and potentially unblinding information for subjects and investigators should not occur prior to the study being unblinded for the primary analysis of OS except as specified (eg, Section 5.2, Section 9.2.1.2, and Section 10.4.3).

10.4 Planned Analyses

10.4.1 Interim Analyses

A DLT interim safety analysis was planned and conducted by the study team for phase 1b. Data were reviewed by a DLRT.

All analyses prior to the primary OS analysis will be conducted by an external independent biostatistics group and reviewed by the DMC per the DMC charter. The analyses will include safety monitoring, ORR/DCR and OS futility, primary and possibly interim PFS_1, and interim OS analyses. The study team is responsible for conducting the primary analysis of OS and all subsequent analyses.

10.4.1.1 DLT Safety Analysis (Phase 1b)

An interim safety analysis in phase 1b to evaluate DLT included 6 subjects who were eligible for DLT evaluation (see Section 10.1.2 for definition of DLT-evaluable subjects in the DLT Analysis Set). Data were reviewed by a DLRT as summarized in Section 3.1.1.1. Rules for determination of DLTs are described in Section 3.1.1.1.

10.4.1.2 Interim Safety Analysis (Phase 3)

Planned safety monitoring in phase 3 will first occur after approximately 20 and 100 subjects, respectively, have been enrolled in phase 3 and have had an opportunity to be followed for at least 6 weeks after receiving study treatment and approximately every 6 months after the DMC meeting for the futility analysis for ORR and DCR has been completed until the later of the study team's unblinding or the primary analysis of OS. Monitoring guidelines for futility will be provided to the DMC. Additional ad hoc safety and/or efficacy data reviews may be requested by the DMC as needed.

10.4.1.3 Interim iORR and iDCR Futility Analysis (Phase 3)

An interim futility analysis of iORR and iDCR per blinded independent central review using modified irRC-RECIST is planned to include the first 160 subjects (ie, approximately 80 per arm) that have had a chance to be followed for the tumor assessment scheduled at week 24. The analysis will include the first 160 subjects enrolled. All tumor response data will be included up to 26 weeks from the date of first dose of study therapy for the 160th enrolled subject (or randomization date if subject is not dosed). The futility criterion will be based on the Bayesian method.

Beta (8.75, 16.25) and Beta (12.5, 12.5) prior distributions are assumed for the true placebo plus pembrolizumab arm (arm 2) iORR and iDCR in the trial population with means equal to 0.35 and 0.50, respectively, and both with the precision equal to a sample size of 25. Beta (10.08, 10.92) and (14.91, 6.09) prior distributions are assumed for the iORR and iDCR for the combination of pembrolizumab and talimogene laherparepvec (arm 1) with means equal to 0.48 and 0.71, respectively, and both with a concentration parameter of 21. The priors for the combination correspond to the results from a 24-week minimum follow-up analysis of the 21 subjects in the phase 1b part of the study.

Beta posterior distributions for the iORR and iDCR will be calculated for each arm based on the corresponding prior distribution and the observed study iORR and iDCR results. The iORR futility criterion will be a posterior probability < 0.65 of at least a 6% absolute iORR increase (Arm 1 – Arm 2), and the iDCR futility criterion will be a posterior probability < 0.75 of at least a 10% absolute iDCR increase. The DMC will declare the combination therapy futile if both the iORR and iDCR futility criteria are met; however, the DMC's recommendation will be non-binding and therefore the sponsor will make the final decision to terminate the study prematurely.

10.4.1.4 Interim Efficacy and Futility Analysis (Phase 3)

There are **5** planned analysis time points for hypothesis testing, including primary and/or interim analyses of the 5 hypotheses (H): H_1, associated with OS; H_2, PFS by blinded independent central review assessed modified RECIST 1.1; H_3, iPFS by blinded independent central review assessed modified irRC-RECIST; H_4, iCRR by blinded independent central review assessed modified irRC-RECIST; and H_5, OS subgroup excluding IVM1c (Table 10). The analysis times are defined by the following event-driven time points with the DMC responsible for Analyses #1**,** #2**, and #3**.

1. **OS interim analysis and** PFS primary analysis at 407 **PFS** events (DMC).
2. OS interim analysis at 282 events (including a futility analysis) (DMC).
3. **OS interim analysis at 315 events (DMC).**
4. OS primary analysis at 346 events.
5. OS subgroup primary analysis at earlier of 208 events in subgroup or 5 years minimum follow-up.

Note that there is no sequential order in these **5** analysis times (with the exception that Analysis #2 is before Analysis #3**, and Analysis #3 before Analysis #4**). Each analysis time may also include interim or primary analyses for the other endpoints. Endpoints to be analyzed, and the type of analysis (ie, interim or primary), are presented in Table 11 and are dependent on which hypotheses have been rejected. For example, testing for

iCRR and iPFS at an analysis time point will be conditional upon previously rejecting either H_1 or H_2. O'Brien-Fleming group sequential boundaries based on the Lan-DeMets approach (O'Brien and Fleming, 1979) will be used for testing endpoints with interim analyses. Multiple testing procedures will utilize the graphic-based Maurer-Bretz approach (Section 10.5).

The information fractions will be based on the events included at the time of analysis for testing of all time to event endpoint null hypotheses (ie, H_1, H_2, H_3, and H_5) and it will be based on the number of subjects with potential follow-up time of at least 36 weeks for testing the iCRR null hypothesis (ie, H_4). The maximum information for testing iCRR is all randomized subjects. Each analysis time will have a corresponding database snapshot; however, there will not be a separate snapshot for each endpoint tested at the same analysis time.

1. The initial alpha allocation for testing the hypothesis of PFS (H_2) is 0.5% and 4.5% for OS (H_1). There will not be a nominal alpha passed back to H_2 after rejecting H_1 or other hypotheses at any analysis.
2. An interim OS analysis will be performed at Analysis #1 with all death events, regardless if H_2 is rejected. In the event when Analysis #2 occurs prior to Analysis #1, then it will include an interim analysis to test H_2 for PFS (using all PFS events) and, if H_2 is not rejected, it will be tested again at the planned time for Analysis #1. However, if the projected time for achieving 407 PFS events is within 4 months from the projected 282 OS events time, then Analysis #2 will be combined with Analysis #1 and be performed at Analysis #1 using all death events with PFS times censored after the 407th PFS event.
3. At each of the **5** planned analysis times, it will be considered an interim analysis of iCRR and iPFS, rather than the primary analysis, if the maximum information has not been reached for the respective endpoint at that time. For example, if H_3 is tested in an analysis that includes fewer than 256 iPFS events, then it will be an interim analysis of iPFS that includes all observed events; otherwise, it will be the primary analysis with all iPFS times censored after the date of the 256th event. If all randomized subjects do not have at least 36 weeks follow-up in an analysis, then it will be an interim analysis for iCRR only including those subjects with at least 36 weeks follow-up; otherwise, it will be the primary analysis and include all randomized subjects. With the exception of PFS, the hypothesis for an endpoint may be re-tested after its primary analysis using its primary analysis data if alpha is subsequently propagated to it from the rejection of another hypothesis.
4. Assuming Analysis #1 is before Analysis #2, and at Analysis #1 the null hypothesis of PFS (H_2) is rejected, the hypotheses H_3 and H_4 will be tested. H_1 will be tested at Analysis #1 regardless of whether H_2 is rejected. The iPFS (H_3) and iCRR (H_4) can be tested if H_2 is not rejected but H_1 is significant. Likewise, OS subgroup (H_5) can be tested at Analysis #1 if any of the following set of hypotheses are rejected: (1) H_2 and H_3; (2) H_2 and H_4; (3) H_1 and H_3; or (4) H_1 and H_4.

5. If projections indicate 256 iPFS events will occur in the same timeframe as either Analysis #1 or Analysis #2, then the option will be considered to extend the data cutoff to include all 256 iPFS events. In this event, Analysis #1 will have PFS times censored after the 407th PFS event and Analysis #1 or #2 will include all OS events.
6. The OS hypothesis (H_1) will be tested at Analyses #1-**4** with all (Analysis #1) or required number (Analysis #2**,** Analysis #3**, and Analysis #4**) of events in the absence of its prior rejection (or futility at Analysis #2).
7. The OS subgroup hypothesis (H_5) will be tested at the first and all subsequent analysis times when alpha can be propogated to it from the rejection of H_1 or H_2 followed by H_3 and/or H_4. All OS events in the subgroup at the end of 5 years follow-up will be used if 208 events have not been observed. If H_1 is not rejected by Analysis #**4**, it will be tested again using events at Analysis #**4** if alpha can be propogated from the rejection of H_5 at Analysis #**5**.
8. Likewise, H_3 and H_4 may be re-tested if not rejected by their primary analysis using their respective primary analysis data if H_1 is subsequently rejected.

Table 11 illustrates possible hypothesis tests at the **5** planned analyses.

Table 11. Study Analyses and Possible Hypothesis Tests

		Hypothesis Tested (Analysis Type)				
Analysis	**Timing**	**H_1 (OS)**	**H_2 (PFS)**	**H_3 (iPFS)**	**H_4 (iCRR)**	**H_5 (OS subgroup)**
#1	407 PFS events	(IA)	(PA)	If reject H_1 or H_2 (IA if < 256 events)	If reject H_1 or H_2 (IA if includes fewer than all random-ized)	If reject H_2 and either H_3 or H_4, or reject H_1 and either H_3 or H_4 (IA if < 208 events)
#2	282 OS events	(IA)	n/a (IA if Analysis #2 is performed first)	If reject H_1 or H_2 (PA on first 256 events)	If reject H_1 or H_2 (PA if includes all random-ized)	If reject H_2 and either H_3 or H_4, or reject H_1 and either H_3 or H_4 (IA if < 208 events)
#3	**315 OS events**	**(IA)**	**n/a**	**If reject H_1 or H_2 (PA on first 256 events)**	**If reject H_1 or H_2 (PA if includes all randomized)**	**If reject H_2 and either H_3 or H_4, or reject H_1 and either H_3 or H_4 (IA if < 208 events)**
#4	346 OS events	(PA)	n/a	See Analysis #2 **and #3** above	See Analysis #2 **and #3** above	See Analysis #2 **and #3** above

Footnotes defined on next page of table

Table 11. Study Analyses and Possible Hypothesis Tests

		Hypothesis Tested (Analysis Type)				
Analysis	**Timing**	**H_1 (OS)**	**H_2 (PFS)**	**H_3 (iPFS)**	**H_4 (iCRR)**	**H_5 (OS subgroup)**
#5	Earlier of 208 OS events in subgroup or 5 years minimum follow-up	If reject H_2 previously and H_5 (PA at first 346 events)	n/a	See Analysis #2 **and #3** above	See Analysis #2 **and #3** above	See Analysis #2 **and #3** above (PA)

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H = hypothesis; IA = interim analysis; iCRR = complete response rate (by modified irRC-RECIST); iPFS = progression free survival (by modified irRC-RECIST); n/a = not applicable; OS = overall survival; PA = primary analysis; PFS = progression free survival

Futility Analysis for OS

At the 282 OS events interim analysis (ie, Analysis #2), if hypothesis H_1 is not rejected, then an OS futility analysis will be evaluated by the DMC. The interim OS futility analysis will be non-binding and define futility as a conditional power < 10% assuming a constant treatment effect (Denne, 2001); the corresponding OS futility boundary is 0.89, assuming a constant HR = 0.70. OS futility will also be evaluated by the DMC considering a possible non-constant treatment effect that increases over time (eg, a 2-interval model with a cutpoint between 4-8 months and constant treatment effect in each interval, where the second interval has a larger effect than the first one). To limit the probability of futility < 0.02, the futility boundary for the observed HR at 282 OS events analysis will be 0.93. Guidelines for this possible late effect will be provided in the DMC charter amendment. Operating characteristics of the primary analysis of PFS and sequential tests of OS are shown in Table 12 based on the OS events expected at Analysis #1.

Table 12. Analysis Timing, Nominal Significance Levels, and Boundary Properties

Analysis	Data cut-off (mon)	Endpoint (scenario)	Event (% goal)	Efficacy nominal 2-sided α	Futile HR [b]	Prob. Futile [b] H_0	Prob. Futile [b] H_1	Efficacy HR	Power total
PFS PA	**48**	PFS	407 (100)	0.0050				0.76	90%
OS IA_1	**48**	OS (PFS-)	**252** (**73**)[a]	0.**0150**				0.**74**	**66**%
		OS (PFS+)		0.**0173**				0.**74**	**67**%
OS IA_2	**52**	OS (PFS-)	282 (82)	0.**0187**	0.89	84%	2%	0.76	76%
		OS (PFS+)		0.**0212**	0.89	83%	2%	0.76	77%
OS IA_3	**61**	**OS (PFS-)**	**315 (91)**	**0.0261**				**0.78**	**84%**
		OS (PFS+)		**0.0292**				**0.78**	**85%**
OS PA	**75**	OS (PFS-)	346 (100)	0.**0336**				0.80	90%
		OS (PFS+)		0.**0372**				0.80	**90**%

IA = interim analysis; H_0 = null hypothesis; H_1 = alternative hypothesis; HR = hazard ratio; OS = overall survival; PFS = progression free survival; PA = primary analysis. O'Brien-Fleming spending α for OS; futility if conditional power < 10%; H_0: HR = 1 and H_1: HR = 0.67 (PFS) and 0.70 (OS). Testing OS at an overall 2-sided 0.045 if PFS is not significant at 2-sided 0.005 (eg, PFS-); testing OS at 0.05 when all other null hypotheses are rejected (eg, PFS+). [redacted]

[a] The events for OS IA_1 are not pre-determined; the estimates shown are the number expected at the time of PFS PA.
[b] The futile HR and probabilities are shown for the conditional power criterion only which assumes a constant OS effect.

10.4.2 Dose Level Review Team (DLRT)

A DLRT consisting of the Amgen study team, including at least one clinician, safety representative, and biostatistician, at least one representative from the Merck study team, and at least one investigator participating in the study who has recruited subjects into phase 1b, reviewed the safety data to evaluate possible DLT. This team will recommend either to enroll more subjects for DLT evaluation in phase 1b, to prematurely stop enrollment into phase 1b, or to declare that the combination is tolerable and whether to open the phase 3. The DLRT will review additional safety data from subjects enrolled in phase 1b beyond the 6 to 9 DLT evaluable subjects to further assess the overall safety profile of talimogene laherparepvec in combination with pembrolizumab.

10.4.3 Data Monitoring Committee (DMC)

An independent DMC which includes two clinicians and a biostatistician who are external to Amgen and Merck will review data from the phase 3 interim analyses prior to the primary analysis of OS (see Section 10.4.1 interim analysis for details). All available safety data from the phase 1b part of the study will also be provided to DMC at the time of the first planned interim safety analysis (ie, at 20 subjects trigger) in phase 3. The DMC will be governed by a detailed DMC charter. Additional DMC safety analyses may be performed if recommended by the DMC based on results from the planned analyses or if requested by the clinical study team.

10.4.4 Primary Analysis

This section describes the timing of the primary analysis of phase 1b and 3, respectively. The clinical study report (CSR) will be written based on the results from the OS primary analysis for phase 3, which will also include safety data from subjects in phase 1b. However, a CSR will be prepared should there be a decision for unblinding the study team based on early stopping for safety, efficacy, or futility (Section 10.4.1). Amgen senior management will make the decision to unblind the study team based on the DMC's recommendations; however, only a subset of the study team will be unblinded prior to the OS primary analysis.

10.4.4.1 Primary Analysis Phase 1b

The goal of the primary analysis is to determine the safety and tolerability of talimogene laherparepvec in combination with pembrolizumab as assessed by incidence of DLT. The primary analysis will occur when the last subject enrolled in the phase 1b has had the opportunity to be on treatment for at least 6 weeks from the initial dosing of pembrolizumab. To evaluate secondary objectives, the phase 1b will be re-analyzed

after the last subject has had a chance to be followed for 24 weeks from the initiation of pembrolizumab and at the time of the phase 3 OS primary analysis.

10.4.4.2 Primary Analysis Phase 3

Phase 3 will evaluate the efficacy as assessed by PFS and OS of talimogene laherparepvec with pembrolizumab versus placebo with pembrolizumab in subjects with unresectable, stage IIIB to IVM1c melanoma. The timing of the primary analyses for PFS and OS of phase 3 will be triggered when 407 PFS events and 346 OS events have occurred, respectively.

10.4.5 Final Analysis

The final analysis will occur approximately 5 years (60 months) after the last subject has been enrolled in phase 3. A separate, final analysis CSR will be drafted with the updated results from the final analysis at the completion of the study.

10.5 Planned Methods of Analysis

The DLT analysis set will be used to summarize the subject incidence of DLT for the phase 1b part of the study and the safety analysis set will be used for all other analyses of safety including incidence of treatment-emergent and treatment-related adverse events (all AEs, grade ≥ 3 AEs, SAEs, fatal AEs and AEs defined as events of interest).

For phase 1b, descriptive statistics for ORR, BOR, DCR, DRR, DOR, PFS, and OS will be provided where tumor response evaluations are based on investigator assessments using modified irRC. The analysis will include data from phase 1b subjects in the Safety Analysis Set.

For phase 3, the efficacy analyses will be conducted on the Full Analysis Set. Treatment effects on efficacy endpoints will be evaluated according to the treatment as randomized. Formal treatment comparisons will be performed on the dual primary endpoints and the 3 key secondary endpoints.

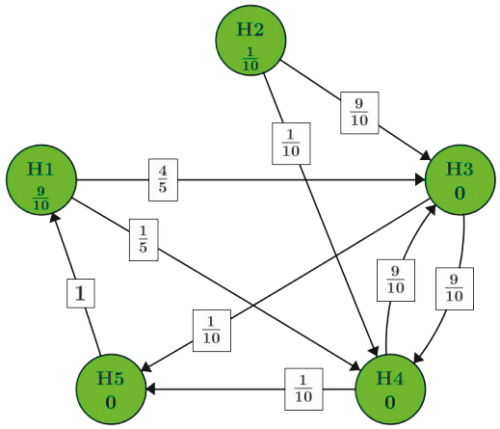
In principle, summary statistics including mean, standard deviation, median, first and third quartiles, will be provided for continuous variables. Frequency and percentage will be summarized by treatment arm for binary and categorical variables. Proportions and the corresponding 95% confidence intervals will be based on normal approximations and the treatment comparison will be based on Cochran-Mantel-Haenszel test. Exact tests will be considered for subgroup analyses when the cell size is too small. Time-to-event endpoints will be estimated using the Kaplan-Meier (KM) estimation. Kaplan-Meier estimates and the 95% confidence intervals for within each treatment arm and

differences between treatment arms by time point will be provided. Standard errors of estimated treatment differences by time point will be calculated using Greenwood's formula (Kalbfleisch and Prentice, 1980). Confidence intervals for the KM quartiles will be provided by treatment arm (Brookmeyer and Crowley, 1982). Log-rank test statistics and associated p-values will also be calculated. Hazard ratios will be estimated using Cox PH models.

10.5.1 Multiple Hypothesis Testing Procedures and Multiplicity Adjustment

Multiple statistical hypothesis tests will be conducted which include testing for primary endpoints of PFS and OS and the 3 secondary endpoints (iCRR, iPFS, and OS in the subgroup excluding disease stage IVM1c) at multiple analysis time points. To control the study-level overall Type I error, a graphic-based multiple testing procedure for group sequential tests for multiple endpoints will be utilized (Maurer and Bretz, 2013). No updated information will be used when a hypothesis is re-tested at a later time point after its primary analysis. A hypothesis can be re-tested repeatedly with a different nominal level that is propagated from rejecting other hypothesis test(s). The following figure illustrates the Maurer-Bretz multiple testing procedure with initial 2-sided α allocation specified as a fraction used for each hypothesis test. Each hypothesis is represented by a circle. A 0 fraction in the circle indicates a hypothesis that is tested conditional on rejection of another hypothesis. The fractions in the square on the directed arrows connecting 2 hypotheses indicate the proportion of α propogated to the next hypothesis test(s) when the current hypothesis is rejected.

Figure 3. Initial Graph of Maurer-Bretz Multiple Testing Procedure



H_1 α = 0.05 × 9/10 = 0.045
H_2 α = 0.05 × 1/10 = 0.005

Due to the nature of Maurer-Bretz multiple testing procedure, the range of nominal levels used for hypothesis tests of OS is beween 4.5% and 5%, and nominal levels used for testing the OS subgroup can range between 0.05% to 5%.

Further details regarding the derivation of nominal significance levels for each hypothesis test at the planned analyses will be provided in the Statistical Analysis Plan.

10.5.2 Primary Endpoint

10.5.2.1 Phase 1b

Subject incidence of DLT: The subject incidence of DLT will be summarized using the DLT analysis set.

10.5.2.2 Phase 3

The primary analyses of the primary endpoints of PFS and OS will be based on stratified log-rank tests as a primary method for testing the null hypothesis of no treatment difference.

The stratification factors will include randomization factors per IVRS and PD-L1 status at baseline (positive vs not positive). Inclusion of PD-L1 is considered in the stratified analysis because PD-L1 overexpression could be a potential prognostic factor, and its pretreatment status may not be able to be confirmed prior for use as a stratification factor at the time of randomization. In order to allow for the use of PD-L1 status in a stratified analysis, indeterminate and missing PD-L1 status will be classified together with the “negative” PD-L1 group. Hazard ratios will be estimated using Cox proportional hazards (PH) models stratified by randomization factors per IVRS and the baseline

PD-L1 status (positive vs not positive). Kaplan-Meier (KM) time to event curves will be presented by the randomized treatment group.

Statistical testing of a treatment effect for PFS and OS will follow the multiple hypothesis testing procedure as described in Section 10.5.

Subgroups and covariates for analyses of PFS and OS will include, but not limited to, disease stage (IIIB/C to IVM1a, IVM1b/c), known PD-L1 status (positive, negative) and prior treatment with BRAF inhibitor.

10.5.3 Secondary Efficacy Endpoints

All secondary endpoints of phase 1b will be descriptive.

Phase 3 analyses of iPFS and OS excluding the disease stage IVM1c subgroup will follow the analysis described for PFS. iCRR by blinded independent central review per modified irRC-RECIST will be treated as a binary endpoint and will be analyzed with a stratified Cochran-Mantel-Haenszel test using the same stratification variables used by the PFS analysis. Following the intent-to-treat principle, subjects who do not have any follow up tumor assessments will be determined to be non-complete responders. Hypothesis testings for iPFS, iCRR, and OS subgroup are described in multiple testing procedures in Section 10.5. Analyses of remaining secondary endpoints in phase 3 will be descriptive.

ORR, DCR, and DRR per modified RECIST and iORR, iDCR, and iDRR per modified irRC-RECIST by blinded independent central review will be summarized by treatment arm as randomized (phase 3). Subjects who do not have any follow up tumor assessments will be classified as not having a response, disease control, or a durable response. DOR (defined as the time from date of the initial response to the date of the initial PD per response criterion or death) will be analyzed among responders and will be estimated using the Kaplan-Meier method.

10.5.4 Safety Endpoints

Treatment emergent adverse events are defined as adverse events that occur after receiving the first dose of study therapy through 30 days after the last dose of study therapy. Subject incidence rates of treatment-emergent adverse events (including all AEs, grade ≥ 3 AEs, SAEs, adverse events of interest and events requiring the discontinuation of study drug, local effects on the tumor [ie, pain, inflammation and ulceration]) will be summarized. Medical Dictionary for Regulatory Activities (MedDRA) will be used to code adverse events to a system organ class (SOC) and a preferred term

within the SOC. The CTCAE version 4.0 will be used to grade severity of adverse events. Adverse events reported beyond 30 days after the last dose will be analyzed separately.

The analyses of safety laboratory endpoints and vital signs will include summary statistics over time by treatment group. Shifts in grades of safety laboratory values between the baseline and the worst on-study value will be tabulated by treatment group.

Summary statistics will also be provided for concomitant medications, dose delay, study treatment discontinuation, overall exposure, and changes in ECOG performance status. Tables and/or narratives of deaths through either the 30 days after the last dose of talimogene laherparepvec or pembrolizumab, whichever is later, will be provided.

The ECG measurements from this clinical study will performed as per standard of care for routine safety monitoring, rather than for purposes of assessment of potential QTc effect. Since these evaluations may not necessarily be performed under the rigorous conditions expected to lead to meaningful evaluation of QTc data, summaries and statistical analyses of ECG measurements are not planned, and these data would not be expected to be useful for meta-analysis with data from other trials.

The qPCR analysis result of talimogene laherparepvec DNA in swab samples taken from cold sore, vesicles and other lesions suspected to be herpetic in origin (if any) will be summarized descriptively. The incidence and percentage of subjects who develop anti-pembrolizumab antibodies (binding and if positive, neutralizing) at any time will be tabulated.

Potential or known unintended exposure to talimogene laherparepvec, related suspected signs or symptoms, and detection of talimogene laherparepvec in a subject's household member, caregiver, or healthcare provider will be reported.

10.5.5 Patient Reported Outcome Endpoints and Analyses

The PRO analyses will be conducted for subjects in the PRO **population**. Summary scores at each assessment and changes from baseline of PROs as assessed by EQ-5D-3L and the QLQ-C30 questionnaires will be reported. Changes from baseline will be summarized and at specified time points of interest, differences between treatment groups for each defined score will be analyzed. For the EORTC QLQ-C30 questionnaire, each of the 5 functional scales, 9 symptom scales, and a GHS/QoL subscale (secondary endpoint) will be summarized similarly. **For the EQ-5D-3L questionnaire, 2 scores will be estimated: the utility score calculated from the**

5 domains using a scoring algorithm, and the VAS score based on the 0 to 100 feeling thermometer. Details of all the PRO analyses will be provided in the **PRO supplemental** statistical analysis plan.

10.5.6 Health State Utility Estimates

For the EQ-5D-3L questionnaire, 2 scores will be estimated: the utility score calculated from the 5 domains using a scoring algorithm, and the VAS score based on the 0-100 feeling thermometer. The calculation of scores and methods for handling missing data will be based on the questionnaire's standard scoring guidelines. Details for deriving the HSU estimates will be provided in the statistical analysis plan.

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

An initial sample informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the template are to be communicated formally in writing from the Amgen Clinical Study Manager to the investigator. The written informed consent document is to be prepared in the language(s) of the potential patient population.

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any investigational products are administered.

The investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study. If the subject agrees to such notification, the investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record.

The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician are to be documented in the subject's medical records, and the informed consent form is to be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the subject.

If a potential subject is illiterate or visually impaired, the investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood.

11.2 Institutional Review Board/Independent Ethics Committee

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material must be submitted to the IRB/IEC for written approval. A copy of the written approval of the protocol and informed consent form must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

The investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent document. The investigator is to notify the IRB/IEC of deviations from the protocol or serious adverse events occurring at the site and other AE reports received from Amgen, in accordance with local procedures.

The investigator is responsible for obtaining annual IRB/IEC approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB/IEC continuance of approval must be sent to Amgen.

11.3 Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen.

- Subjects are to be identified by a unique subject identification number.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.
- On the CRF demographics page, in addition to the unique subject identification number, include the age at time of enrollment.
- For serious adverse events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and date of birth (in accordance with local laws and regulations).
- Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in confidence by the investigator, except as described below.

In compliance with Federal regulations/International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s),

and the IRB/IEC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information.

11.4 Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multi-center studies, the coordinating investigator.

The coordinating investigator, identified by Amgen, will be any or all of the following:

- a recognized expert in the therapeutic area
- an investigator who provided significant contributions to either the design or interpretation of the study
- an investigator contributing a high number of eligible subjects

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

If Amgen amends the protocol, agreement from the investigator must be obtained. The IRB/IEC must be informed of all amendments and give approval. The investigator must send a copy of the approval letter from the IRB/IEC to Amgen.

Amgen reserves the right to terminate the study at any time. Both Amgen and the investigator reserve the right to terminate the investigator's participation in the study according to the study contract. The investigator is to notify the IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to Amgen.

Subjects may be eligible for continued treatment with Amgen investigational product talimogene laherparepvec by an extension protocol or as provided for by the local country's regulatory mechanism. However, Amgen reserves the unilateral right, at its sole discretion, to determine whether to supply Amgen investigational product talimogene laherparepvec and by what mechanism, after termination of the study and before the product is available commercially.

12.2 Study Documentation and Archive

The investigator is to maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Amgen Delegation of Authority Form.

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

In this study, the IVRS captures the following data points and these are considered source data: subject identification number and randomization number.

CRF entries may be considered source data if the CRF is the site of the original recording (ie, there is no other written or electronic record of data).

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities.

Elements to include:

- Subject files containing completed CRFs, informed consent forms, and subject identification list.
- Study files containing the protocol with all amendments, investigator's brochure, copies of prestudy documentation, and all correspondence to and from the IRB/IEC and Amgen.
- Investigational product-related correspondence including Proof of Receipts (POR), Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable.

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

Retention of study documents will be governed by the Clinical Trial Agreement.

12.3 Study Monitoring and Data Collection

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, CRFs and other pertinent data) provided that subject confidentiality is respected.

The Amgen clinical monitor is responsible for verifying the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical

research. The clinical monitor is to have access to subject medical records and other study-related records needed to verify the entries on the CRFs.

The investigator agrees to cooperate with the clinical monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Compliance Auditing function (or designees). Inspection of site facilities (eg, pharmacy, protocol-required therapy storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the CRFs must be maintained and readily available.
- Updates to CRFs will be automatically documented through the software's "audit trail".
- To ensure the quality of clinical data across all subjects and sites, a clinical data management review is performed on subject data received at Amgen. During this review, subject data are checked for consistency, omissions, and any apparent discrepancies. In addition, the data are reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process and/or data queries are created in the EDC system database for site resolution and subsequently closed by the EDC system or by an Amgen reviewer.
- The investigator signs only the Investigator Verification Form for this electronic data capture study. This signature indicates that investigator inspected or reviewed the data on the CRF and the data queries, and agrees with the content.

12.4 Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including subjects not receiving protocol-required therapies) as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Assessments (Table 5 and Table 6), the investigator can search publicly available records [where permitted]) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

12.5 Language

CRFs must be completed in English. TRADENAMES® (if used) for concomitant medications may be entered in the local language. Consult the country-specific language requirements.

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

12.6 Publication Policy

To coordinate dissemination of data from this study, Amgen may facilitate the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other investigators and to collaborate with authors and Amgen staff, as appropriate, as defined in the Publication Charter. Membership on the committee (both for investigators and Amgen staff) does not guarantee authorship. The criteria described below are to be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct of Reporting, Editing, and Publications of Scholarly Work in Medical Journals, which states: Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, 3 and 4.

When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above. Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship. All persons designated as authors should qualify for authorship, and all those who qualify should be listed. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review. The Clinical Trial Agreement among the

institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

12.7 Compensation

Any arrangements for compensation to subjects for injury or illness that arises in the study are described in the Compensation for Injury section of the Informed Consent that is available as a separate document.

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14. APPENDICES

Appendix A. Additional Safety Assessment Information

Adverse Event Grading Scale

The Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 is available at the following location:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Appendix B. Sample Serious Adverse Event Report Form

Completion Instructions - Electronic Adverse Event Contingency Report Form
(For use for clinical trial studies using Electronic Data Capture [EDC])

NOTE: This form is to be used under restricted conditions outlined on page 1 below. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

General Instructions

The protocol will provide instruction on what types of events to report for the study. This form is to be used ONLY to report events that must be captured in the Amgen safety database. *Indicates a mandatory field.

Types of Events to be reported on this form

- **Serious Adverse Events (regardless of causal relationship to IP)**

1. **Site Information**

   Site Number* – Enter your assigned site number for this study

   Investigator*, Country*, Reporter*, Phone No., and Fax No. – Enter information requested

2. **Subject Information**

   Subject ID Number* – Enter the entire number assigned to the subject

   Age at event onset, Sex, and Race – Enter the subject's demographic information

   End of Study date – If the subject has already completed the study or terminated the study early, enter the End of Study date

If you are submitting follow-up information to a previous report, provide the serious adverse event term for the previous report as well as the start date for the initial event.

3. **Serious Adverse Event**

   Provide the date the Investigator became aware of this Information

   Serious Adverse Event Diagnosis or Syndrome* –

   - If the diagnosis is known, it should be entered. Do not list all signs/symptoms if they are included in the diagnosis.
   - If a diagnosis is not known, the relevant signs/symptoms should be entered.
   - If the event is fatal, the cause of death should be entered and autopsy results should be submitted, when available.

   Date Started* – Enter date the adverse event first started (not the date on which the event met serious criteria)rather than the date of diagnosis or hospitalizion. . **This is a mandatory field.**

   Date Ended – Enter date the adverse event ended and not the date when the event no longer met serious criteria. If the event has not ended at the time of the initial report, a follow-up report should be completed when the end date is known. If the event is fatal, enter the date of death as the end date.

   If event occurred before the first dose of Investigational Product (IP)/drug under study, add a check mark in the corresponding box.

   Is event serious?* – Indicate Yes or No. This is a mandatory field.

   Serious Criteria Code* – This is a mandatory field for serious events. Enter all reasons why the reported event has met serious criteria:

   - Immediately life-threatening – Use only if the subject was at immediate risk of death from the event as it occurred. Emergency treatment is often required to sustain life in this situation.
   - If the investigator decides an event should be reported in an expedited manner, but it does not meet other serious criteria, "Other Medically Important Serious Event" may be the appropriate serious criterion.

   Relationship to IP – The Investigator must determine and enter the relationship of the event to the IP at the time the event is initially reported. **This is a mandatory field.**

   Relationship to Amgen device* – The Investigator must determine and enter the relationship of the event to the Amgen device (e.g. prefilled syringe, auto-injector) at the time the event is initially reported. **If the study involves an Amgen device, this is a mandatory field. This question does not apply to non-Amgen devices used in the study (e.g. heating pads, infusion pumps)**

   Outcome of Event* – Enter the code for the outcome of the event at the time the form is completed. **This is a mandatory field.**

   - Resolved – End date is known
   - Not resolved / Unknown – End date is unknown
   - Fatal – Event led to death

   If event is related to a study procedure, such as a biopsy, radiotherapy or withdrawal of a current drug treatment during a wash-out period, add a check mark to the corresponding box. This does not include relationship to IP or concomitant medication – only diagnostic tests or activities mandated by the protocol.

4. **Hospitalization**

   If the subject was hospitalized, enter admission and discharge dates. Hospitalization is any in-patient hospital admission for medical reasons, including an overnight stay in a healthcare facility, regardless of duration. A pre-existing condition that did not worsen while on study which involved a hospitalization for an elective treatment, is not considered an adverse event. Protocol specified hospitalizations are exempt.

Completion Instructions - Electronic Adverse Event Contingency Report Form (for use for Studies using Electronic Data Capture [EDC])

Note, this form is to be used under restricted conditions outlined on page 1 of the form. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

At the top of Page 2, provide your Site Number and the Subject ID Number in the designated section.

5. **IP Administration including Lot # and Serial # when known / available.**

   Blinded or open-label – If applicable, indicate whether the investigational product is blinded or open-label

   Initial Start Date – Enter date the product was first administered, regardless of dose.

   Date of Dose Prior to or at the time of the Event – Enter date the product was last administered prior to, or at the time of, the onset of the event.

   Dose, Route, and Frequency at or prior to the event – Enter the appropriate information for the dose, route and frequency at, or prior to, the onset of the event.

   Action Taken with Product – Enter the status of the product administration.

6. **Concomitant Medications**

   Indicate if there are any medications.

   Medication Name, Start Date, Stop Date, Dose, Route, and Frequency – Enter information for any other medications the subject is taking. Include any study drugs not included in section 5 (Product Administration) such as chemotherapy, which may be considered co-suspect.

   Co-suspect – Indicate if the medication is co-suspect in the event

   Continuing – Indicate if the subject is still taking the medication

   Event Treatment – Indicate if the medication was used to treat the event

7. **Relevant Medical History**
   Enter medical history that is relevant to the reported event, not the event description. This may include pre-existing conditions that contributed to the event allergies and any relevant prior therapy, such as radiation. Include dates if available.

8. **Relevant Laboratory Tests**

   Indicate if there are any relevant laboratory values.

   For each test type, enter the test name, units, date the test was run and the results.

9. **Other Relevant Tests**

   Indicate if there are any tests, including any diagnostics or procedures.

   For each test type, enter the date, name, results and units (if applicable).

At the top of Page 3, provide your Site Number and the Subject ID Number in the designated section.

10. **Case Description**

    Describe Event – Enter summary of the event. Provide narrative details of the events listed in section 3. Include any therapy administered, such as radiotherapy; (excluding medications, which will be captured in section 6). If necessary, provide additional pages to Amgen.

Complete the signature section at the bottom of page 3 and fax the form to Amgen. *If the reporter is not the investigator, designee must be identified on the Delegation of Authority form.*

AMGEN
Study # 20110265
Talimogene laherparepvec

Electronic Serious Adverse Event Contingency Report Form

For Restricted Use

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site
☐ Is not yet available for this study
☐ Has been closed for this study

<<For completion by COM prior to providing to sites: SELECT OR TYPE IN A FAX#>>

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Age at event onset	Sex	Race	If applicable, provide End of Study date
		☐F ☐M		

If this is a follow-up to an event reported in the **EDC system (eg, Rave)**, provide the adverse event term: _____
and start date: Day ____ Month _____ Year _____

3. SERIOUS ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day____ Month____ Year_____

Serious Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report *List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of IP	Is event serious?	If serious, enter Serious Criteria code (see codes below)	Relationship: Is there a reasonable possibility that the Event may have been caused by IP or an Amgen device used to administer the IP? Talimogene laherparepvec No Yes / Pembrolizumab No Yes / <Device> No Yes / <Device> No Yes	Outcome of Event -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy
				☐Yes ☐No				
				☐Yes ☐No				
				☐Yes ☐No				

Serious Criteria: **01** Fatal; **02** Immediately life-threatening; **03** Required/prolonged hospitalization; **04** Persistent or significant disability /incapacity; **05** Congenital anomaly / birth defect; **06** Other medically important serious event

4. Was subject hospitalized or was a hospitalization prolonged due this event? ☐No ☐Yes If yes, please complete all of Section 4

Date Admitted Day Month Year	Date Discharged Day Month Year

5. Was IP/drug under study administered/taken prior to this event? ☐No ☐Yes If yes, please complete all of Section 5

IP/Amgen Device:		Date of Initial Dose Day Month Year	Prior to, or at time of Event: Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
Talimogene laherparepvec	☐blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
Pembrolizumab	☐blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

AMGEN
Study # 20110265
Talimogene laherparepvec

Electronic Serious Adverse Event Contingency Report Form

For Restricted Use

Site Number	Subject ID Number

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Medications? ☐ No ☐ Yes If yes, please complete:

Medication Name(s)	Start Date Day Month Year	Stop Date Day Month Year	Co-suspect No✓	Co-suspect Yes✓	Continuing No✓	Continuing Yes✓	Dose	Route	Freq.	Treatment Med No✓	Treatment Med Yes✓

7. RELEVANT MEDICAL HISTORY ***(include dates, allergies and any relevant prior therapy)***

8. RELEVANT LABORATORY VALUES ***(include baseline values)*** Any Relevant Laboratory values? ☐ No ☐ Yes If yes, please complete:

Date Day Month Year	Test											
	Unit											

9. OTHER RELEVANT TESTS ***(diagnostics and procedures)*** Any Other Relevant tests? ☐ No ☐ Yes If yes, please complete:

Date Day Month Year	Additional Tests	Results	Units

AMGEN Study # 20110265 Talimogene laherparepvec	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

10. CASE DESCRIPTION ***(Provide narrative details of events listed in section 3)*** Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.

Signature of Investigator or Designee - _____ *I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.*	Title	Date

Appendix C. Pregnancy and Lactation Notification Worksheets

Amgen Proprietary - Confidential

AMGEN® Pregnancy Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20110265

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 age (at onset):** ____(in years)

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 last menstrual period (LMP) mm_____/ dd_____/ yyyy_____ ☐Unknown ☐ N/A

Estimated date of delivery mm_____/ dd_____/ yyyy_____

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:** _____

FORM-115199 Version 1.0 Effective Date: 24-Sept-2018

AMGEN® Lactation Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20110265

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 age (at onset):**____(in years)

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:** _____

FORM-115201 Version 1.0 Effective Date: 24-Sept-2018

Appendix D. Modified Immune-related Response Criteria (irRC) for Review of Disease Response in Phase 1b

A systematic tumor response criteria designated immune-related response criteria (irRC) was defined by Wolchok et al, 2009, in an attempt to capture additional tumor response patterns observed with immunotherapy in advanced melanoma beyond those described by the Response Evaluation Criteria in Solid Tumors (RECIST) or the World Health Organization (WHO) criteria. A modified version of the irRC will be employed in the phase 1b part of the study.

Method of Measurement of Melanoma Tumor Lesions

Clinical Examination Using Caliper: All measurements will be determined using a ruler or calipers and reported in metric notation (mm) and will be recorded bi-dimensionally. Clinical lesions will only be considered measurable when they are superficial and can be accurately and serially measured in at least 2 dimensions and for which the longest diameter is ≥ 5 mm as assessed using calipers (eg, superficial cutaneous and subcutaneous melanoma lesions). [Note: When a lesion can be accurately evaluated by both, clinical examination and imaging, imaging evaluations should be undertaken since it is more objective].

Photographs: Photographic imaging of up to 5 (maximum 5 per organ) visible (ie, visible protrusion from skin surface) cutaneous and subcutaneous measurable tumor lesions will performed to evaluate tumor response for cutaneous and subcutaneous lesions. All measurements will be determined using a ruler or calipers and reported in metric notation (mm) and will be recorded bi-dimensionally. Photographed cutaneous and subcutaneous lesions will only be considered measurable when they are visible (ie, visible protrusion from skin surface) and can be accurately and serially photographed and measured in at least 2 dimensions and for which the longest diameter is ≥ 5 mm as assessed using calipers. [Note: When a lesion can be accurately evaluated by both, radiographic imaging and photographs, radiographic imaging evaluations should be undertaken].

CT scans (or MRI): Computed tomography (CT) scans by contrast-enhanced or spiral scan (or magnetic resonance imaging [MRI] scan) will be performed to evaluate tumor response for visceral or nodal/soft tissue disease (including lymph nodes). Measurability of lesions on CT scan is based on the assumption that CT slice thickness is 5 mm or less. MRI is acceptable to assess disease extent if used throughout the study.

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. A switch from contrast enhanced CT to noncontrast CT or to MRI (or vice versa) should not preclude response assessment if, in the judgment of the site radiologist, there is no significant difference in the assessment by changing modalities. This may occur if a subject has developed a medical contraindication to intravenous contrast for CT scans while on trial. This change would require the preapproval of the sponsor medical monitor.

Positron Emission Tomography (PET)/CT Scans: If a combined PET/CT scan is performed at the discretion of the investigator, the CT portion of that exam should not be substituted for the dedicated CT exams required by this protocol. The PET portion of the CT may introduce additional data which may bias the investigator assessment of response if it is not routinely or serially performed. However, if the investigator or the site radiologist can document that the CT performed as part of a PET/CT is of identical diagnostic quality to a diagnostic CT (with intravenous and oral contrast) then the CT portion of the PET/CT can be used for tumor measurements.

Ultrasound: Ultrasound may be used to assess superficial palpable lymph nodes and subcutaneous lesions where ultrasound provides a more accurate measure than clinical measurement or CT. In addition, ultrasound can be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination. However, if ultrasound is not useful in assessment of lesion size it must not be used to as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

Measurement of Lesions

Measurability is defined by the ability to measure a lesion bi-dimensionally with surface area determined by multiplying the longest diameter by the diameter perpendicular to the longest diameter as defined below. An individual lesion measure is therefore provided by the product of a tumors longest diameter and the diameter perpendicular to that.

All measurements will be determined using a ruler or calipers and reported in metric notation (mm) and will be recorded bi-dimensionally.

Definitions of Measurable and Nonmeasurable Lesions

At baseline, lesions are categorized as measurable or nonmeasurable according to the following definitions:

Measurable Lesions:

Measurable lesions are defined at baseline as lesions that can be accurately and serially measured in at least 2 dimensions and for which the longest diameter is:

- ≥ 10 mm as measured by CT scan (CT scan slice thickness no greater than 5 mm) or MRI for visceral or nodal/soft tissue disease (including lymph nodes)
- ≥ 5 mm caliper measurement by clinical exam for superficial cutaneous or subcutaneous melanoma lesion as measured by caliper

Nonmeasurable:

All other lesions, including small lesions (longest diameter < 10 mm by CT/MRI for visceral or nodal/soft tissue disease [including lymph nodes] or < 5-mm caliper measurement by clinical exam or photographs for superficial cutaneous and subcutaneous melanoma lesions) and other truly nonmeasurable lesions are considered non-measurable and characterized as nonindex lesions. Other examples of nonmeasurable lesions include some bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of the skin or (lymphangitis cutis/pulmonis), and groups of lesions that are small and numerous.

Bone Lesions:

- Bone scans, PET scans or plain films are not considered adequate imaging techniques to measures bone lesions. However, these techniques can be used to confirm the presence or absence of bone lesions.
- Lytic bone lesions or mixed Lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging technique such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are not nonmeasurable.

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same subject, these are preferred for selection as index lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated in a previously irradiate area, or an area subject to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

Measureable Tumor Assessment/Burden:

Baseline Documentation of "Index Lesions":

All baseline evaluations should be performed as close as to the enrollment or randomization and never more than 4 weeks (ie, 28 days) prior to enrollment/randomization.

At baseline up to 5 cutaneous or subcutaneous lesions and 10 visceral lesions, a maximum of 5 per organ, will be chosen to measure over the course of therapy. The distribution of these index lesions should be representative of the subject's overall disease status. Index lesions should be selected on the basis of their size (lesions with longest bi-dimensionally perpendicular diameters) and suitability for accurate repeated measurements by imaging techniques (CT, MRI or US) and/or other method such as clinical exam or photographs, if tumor lesions cannot be accurately evaluated by imaging techniques.

The sum of the products of the two largest of perpendicular diameters (SPD) of all index lesions will be calculated and reported.

Baseline Documentation of "Non-index Lesions": All other lesions (or sites of disease), including any measurable lesions beyond the maximum number of 5 cutaneous lesions and 10 visceral lesions (maximum 5 lesions per organ) that that were not chosen as index lesions will be identified as nonindex lesions. Measurable nonindex lesions should also be recorded and assessed qualitatively over the course of therapy.

Follow-up:

At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions (accurately and serially measured in at least 2 dimensions and for which the longest diameter is ≥ **10** mm) are added together to provide the total tumor burden. A maximum of up to 5 new cutaneous or subcutaneous lesions and 10 visceral lesions (maximum 5 new lesions per organ) may be identified. If measurable new lesions are present exceeding the organ-specific or total maximum, the lesions should be selected on the basis of their size (lesions with longest bi-dimensionally perpendicular diameters) and suitability for accurate repeated measurements by imaging techniques (CT, MRI or US) and/or other method such as clinical exam or photographs.

Tumor Burden = SPDindex lesions + SPDnew, measurable lesions.

Non-measurable nonindex disease measurements are not required and these lesions should be followed as “present”, “absent”, or in rare cases “unequivocal progression”.

For index and new measurable nodal lesions < 10 mm, the measurement should be recorded as the 0 x 0 mm instead of the actual measurement.

Response Criteria

Evaluation of Objective Response Rate:

The subject response will be assessed based on the response of the index lesions and the presence or absence of new measurable lesions, and, in the case of CR, the presence or absence of nonindex lesions. The overall response is derived from time-point response assessments (based on tumor burden) as described in Table 13 and Table 14.

Table 13. Definition of Measurable Tumor Response

Complete Response (CR):	Complete disappearance of all lesions (whether measurable or not, and no new lesions) confirmation by a repeat, consecutive assessment no less than 4 weeks (28 days) from the date first documented.
Partial Response (PR):	Decrease in tumor burden ≥ 50% relative to baseline confirmed by a consecutive assessment at least 4 weeks (28 days) after first documentation.
Progressive Disease (PD):	Increase in tumor burden ≥ 25% relative to nadir (minimum recorded tumor burden) confirmation by a repeat, consecutive assessment no less than 4 weeks (28 days) from the date first documented PD.
Stable Disease (SD):	Not meeting criteria for CR or PR, in absence of PD.
Unevaluable (UE):	Any lesion present at baseline which was not assessed or was unable to be evaluated leading to an inability to determine the status of that particular tumor for that time point.
Not Applicable (NA)	No index lesions were identified at baseline
Not Done (ND)	Radiographic image, photographic image or clinical measurement were not performed at this time point to evaluate the index lesions

Table 14. Matrix for Determining the Overall Response at Each Assessment Point

Measurable Response	Non-measurable Response		Overall Response
Index and new, measurable lesions (tumor burden)[a], %	Non-index	New, non-measurable lesions	Using irRC
↓100	Absent/NA[d]	Absent	CR[b]
↓100	Present/ND/**UE**	Any	PR[b]
↓100	Unequivocal progression	Any	PR[b]
↓≥ 50	Absent/Present/NA[d]/ND/**UE**	Any	PR[b]
↓≥ 50	Unequivocal progression	Any	PR[b]
↓< 50 to < 25↑	Absent/Present/NA[d]/ND/**UE**	Any	SD
↓< 50 to < 25↑	Unequivocal progression	Any	SD
≥ 25	Any	Any	PD[b]
UE	Any	Any	UE
ND	Any	Any	UE
NA[c]	Any	Any	UE

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; UE = unevaluable; ND = not done; NA = not applicable.

[a] Decrease disease relative to baseline, including new measurable lesions only (> 5x5mm).

[b] Assuming response (CR or PR) or progression are confirmed by a second, consecutive assessment at least 4 weeks (28 days) apart.

[c] No index lesions identified at baseline. When a patient has only nonmeasurable disease (ie, no index lesions identified at baseline) the response will be unevaluable.

[d] No non-index lesions identified at baseline.

Determination of irRC BOR is based on changes in total tumor burden from the baseline (nadir, for PD) tumor assessment, regardless of any initial increase in baseline lesions or the appearance of new lesions.

Subjects are considered to have PR or SD even if new lesions were present, as long as they met the respective thresholds of response as described in Table 14.

Response Confirmation

To be assigned a status of CR or PR changes in tumor measurements must be confirmed by consecutive repeat assessments performed no less than 4 weeks (28 days) after the criteria for response are first met.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR status.

If a subject is classified as having PD at a post baseline tumor assessment, then confirmation of PD by a second consecutive assessment in the absence of clinical instability (Section 3.1.3.1) is required. The definition of confirmation of progression represents an increase in tumor burden ≥ 25% compared with the nadir at two consecutive time points at least 4 weeks (28 days) apart.

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of PD at the time should have the reason for treatment discontinuation classified as "nonconfirmed PD." In this case PD cannot be assigned at the time as the overall objective tumor response. Every effort should be made to document the objective progression even after discontinuation of treatment.

A best overall response of SD requires a visit response of SD or better no earlier than **84** days after the date of enrollment; otherwise the overall response will be UE.

Subjects who have had a procedure to completely/partially resect a lesion will be evaluated as follows:

The procedure itself and all post-procedure lesion assessments should always be recorded in the CRF. A completely resected lesion should be assigned a default code of 0 x 0 mm (for index and new measurable lesions) or "absent" (for non-index and new non-measurable lesions). A partially resected lesion should be assigned its measurement post-procedure (for index or new measurable lesions) or "present" (for non-index or new non-measurable lesions). If the resected lesion contained no melanoma under pathology evaluation, subsequent tumor assessments post-procedure may be used for tumor burden calculations and/or determination of response. If the resected lesion contained melanoma or pathology results were unknown, the recorded tumor assessments post-procedure may be used for tumor burden calculations, but determination of response will be considered unevaluable (UE) for response except in the case of PD.

If the new tumor burden post-procedure is lower than the nadir before the procedure, then the new nadir will be set to the post-procedure tumor burden. Otherwise, the previous pre-procedure nadir will be retained as the nadir. Subsequent assessments for PD will be determined from the nadir.

Appendix E. Eastern Cooperative Oncology Group Performance Status Scale

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, ie, light housework or office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about > 50% of waking hours.
3	Capable of only limited self-care, confined to a bed or chair > 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Appendix F. Modified irRC-RECIST Guidelines for Assessment of Disease Response in Phase 3

Immune-related Response Criteria (irRC) simulating Response Evaluation Criteria in Solid Tumors version (RECIST) 1.1 [irRC-RECIST] defined by Nishino et al, 2014 will employed in the phase 3 to account for unique tumor response characteristics observed with immunotherapies to enable treatment beyond progression, if the subject is clinically stable. These criteria are modified to increase the total number of target lesions to 10 with a maximum of 5 target lesions per organ. Similarly the total number of new measurable lesions is also increased to 10 with a maximum of 5 target lesions per organ. Target lesions are be measurable by CT or MRI only. Otherwise, these guidelines will follow irRC simulating RECIST 1.1 defined by Nishino et al, 2014.

Method of Measurement of Melanoma Tumor Lesions:

Photographs: Photographs of all (ie, visible protrusion from skin surface) cutaneous and subcutaneous tumor lesions not detectable on radiographic imaging will performed to evaluate tumor response for non-target cutaneous and subcutaneous lesions. Photographed cutaneous and subcutaneous lesions will not need to be measured and will be considered non-target. [Note: When a lesion can be accurately evaluated by both photographs and radiographs, radiographic imaging and photographs, radiographic imaging evaluations should be undertaken].

CT scans (or MRI): Computed tomography (CT) scans by contrast-enhanced or spiral scan (or magnetic resonance imaging [MRI] scan) will be performed to evaluate tumor response for visceral or nodal/soft tissue disease (including lymph nodes). Measurability of lesions on CT scan is based on the assumption that CT slice thickness is 5 mm or less. MRI is acceptable to assess disease extent if used throughout the study.

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. A switch from contrast enhanced CT to noncontrast CT or to MRI (or vice versa) should not preclude response assessment if, in the judgment of the site radiologist, there is no significant difference in the assessment by changing modalities. This may occur if a subject has developed a medical contraindication to intravenous contrast for CT scans while on trial. This change would require the preapproval of the sponsor medical monitor.

Positron Emission Tomography (PET)/CT Scans: If a combined PET/CT scan is performed at the discretion of the investigator, the CT portion of that exam should not be substituted for the dedicated CT exams required by this protocol. The PET portion of the CT may introduce additional data which may bias the investigator assessment of response if it is not routinely or serially performed. However, if the investigator or the site radiologist can document that the CT performed as part of a PET/CT is of identical diagnostic quality to a diagnostic CT (with intravenous and oral contrast) then the CT portion of the PET/CT can be used for tumor measurements.

Ultrasound is not appropriate for measurement of target lesions due to higher variability in measurement technique compared to CT or MRI. Any new lesions identified by ultrasound will need to be confirmed by CT or MRI. At baseline, lesions are categorized as Measurable or Non-Measurable according to the following definitions:

Measurable Lesions:

Measurable lesions are defined at baseline as lesions that can be accurately measured in at least one dimension (ie, longest diameter for non-nodal lesions and short axis for lymph nodes will be measured and followed) with a minimum size of:

- ≥ 10 mm by CT scan (CT scan slice thickness no greater than 5 mm) or MRI.
- A lymph node must be ≥ 15 mm in short axis when assessed by CT scan or MRI.

Scan slices should be 3 to 5 mm and not exceed 5 mm. Target lesions must not be chosen from a previously irradiated field unless there has been documented tumor progression in that field prior to enrollment. The distribution of the target lesions should be representative of the subject's overall disease (eg, largest lesions per organ).

Non-Measurable Tumor Lesions:

Indeterminate lesions which may or may not be cancer should not be considered non-measurable tumor lesions. These lesions must all be considered cancer. All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 mm but < 15 mm short axis) and other truly non-measurable lesions are considered non-measurable and characterized as non-target lesions. This will include any measurable lesions beyond the maximum number of 10 total or 5 per organ at each time point that were not chosen as target lesions. Other examples of non-measurable lesions include some bone lesions*, leptomeningeal disease, inflammatory breast disease, lymphangitic involvement of the skin or (lymphangitis cutis/pulmonis), and groups of lesions that are small and numerous.

***Bone Lesions:**

- Bone scans, PET scans or plain films are not considered adequate imaging techniques to measures bone lesions. However, these techniques can be used to confirm the presence or absence of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging technique such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above. Only the soft tissue component of the bone lesion should be measured.
- Blastic bone lesions should not be selected as non-measurable at baseline since many blastic bone lesions might be benign. However, if new blastic lesions appear and are clearly progressing, they may be considered as new non-measurable lesions.

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable or non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.
- If a cancerous cystic lesion has both cystic and solid components, the entire lesion should be measured across both components without excluding the cystic component.

Lesions with Prior Local Treatment:

- Tumor lesions situated in a previously irradiated area, or an area subject to other loco-regional therapy, are not considered measurable unless there has been demonstrated progression in the lesion.

Baseline Documentation of "Target" and "Non-Target" Lesions:

Baseline evaluations will be used to prospectively identify all sites of disease present as close as possible to the enrollment and never more than 4 weeks before the enrollment date. Sites of disease will be characterized as either target or non-target lesions.

Baseline Documentation of Target Lesions:

Up to 10 target lesions (a maximum of 5 per organ) will be chosen to measure over the course of therapy. Pathological lymph nodes that are defined as measurable must meet the criterion of a short axis of ≥ 15 mm by CT scan in order to be identified as target lesions. Lesions that only appear on photography and not on radiographic imaging should not be selected as target lesions.

The distribution of these target lesions should be representative of the subject's overall disease status. Target lesions should be selected on the basis of their size (lesions with longest diameter) and suitability for accurate repeated measurements by imaging

techniques. There may be circumstances where the larger lesions are not appropriate for accurate repeated measurements (eg, proximity to diaphragm that may lead to variability between scans depending on respiratory changes), and smaller lesions that are measurable and more accurately assessed may need to be selected for target lesions.

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 of diameters will be used as reference by which to characterize the objective tumor response.

Baseline Documentation of Non-Target Lesions:

All other lesions (or sites of disease), including any measurable lesions that were not chosen as target lesions, cutaneous and subcutaneous lesions on appearing on photography and not radiographic images, and pathological lymph nodes with short axis ≥ 10 mm but < 15 mm, should be identified as non-target lesions. Measurable non-target lesions (ie, those that exceed the maximum 10 target lesions overall or maximum 5 target lesions per organ) should also be recorded and assessed qualitatively over the course of therapy. Non-target disease measurements are not performed, but should be evaluated as 'present,' 'absent,' or in rare cases 'unequivocal progression.' If a significant partial response occurs in a non-target lesion, this should be documented in the comments section.

Follow-up Assessment of Tumor Lesions:

At each subsequent tumor assessment, the sum of diameters of target lesions identified at baseline plus the sum of diameters of up to 10 (maximum 5 per organ) new measurable lesions per time point (ie, and for which the longest diameter is ≥ 10 mm for non-nodal lesions or the short axis is ≥ 15 mm for nodal lesions) are added together to provide the total tumor burden. If more than 10 new measurable lesions total (or 5 per organ) are present at a given time point, the new measurable lesions should be selected on the basis of their size and suitability for accurate repeated measurements by imaging techniques (CT or MRI). If there are lesions beyond of the new measurable lesion limit during the course of the study for one subject, the additional lesions would be considered new non-measurable lesions.

Tumor Burden = sum of diameter of target lesions + sum of diameter of up to 10 (maximum 5 per organ) new, measurable lesions.

Non-target disease measurements are not required and these lesions should be followed as "present", "absent", or "unequivocal progression".

For target lesions that become too small to measure, a value of 5 mm will be assigned. If an actual measurement is able to be provided, that should be recorded, even if it is < 5 mm. If it is in the opinion of the radiologist that the non-nodal lesion has likely disappeared, the measurement should be recorded as "0 mm". Nodal disease should always have the actual short axis measurement recorded even if the nodes regress to below 10 mm on study. For iCR, each node must achieve a short axis <10 mm.

Non-target lesions photographed at baseline should continue to be photographed at subsequent time points if not detected via radiographic imaging.

Response Evaluation:

Evaluation of Objective Response:

The subject response will be assessed based on tumor burden (the sum of diameters of target lesions plus the sum of up to 10 [maximum 5 per organ] new measurable lesions per time point), and, in the case of iCR, the presence of any non-target and/or new non-measurable lesions. The overall response is derived from time-point response assessments as described in Table 15 and Table 16.

Table 15. Definition of Measurable Tumor Response (Baseline Target and New, Measurable Lesions)

Complete Response (iCR):	Disappearance of all lesions (whether measurable or not and whether baseline or new) and confirmation by a repeat, consecutive assessment no less than 4 weeks (28 days) from the date first documented. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (iPR):	Decrease in tumor burden[a] ≥ 30% relative to baseline confirmed by a consecutive assessment at least 4 weeks (28 days) after first documentation
Progressive Disease (iPD):	Increase in tumor burden[a] ≥ 20 % and at least 5 mm absolute increase relative to nadir (minimum recorded tumor burden) confirmation by a repeat, consecutive assessment no less than 4 weeks (28 days) from the date first documented iPD.
Stable Disease (iSD):	Neither sufficient shrinkage to qualify for iCR or iPR nor sufficient increase to qualify for iPD.
Unevaluable (iUE):	Any lesion present at baseline or a new measureable lesion which was not assessed or was unable to be evaluated leading to an inability to determine the status of that particular tumor for that time point. Exception: when iPD is documented based on a partial assessment.

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Footnotes defined on next page of table

Table 15. Definition of Measurable Tumor Response (Baseline Target and New, Measurable Lesions)

Not Applicable (NA)	No target lesions were identified at baseline
Not Done (ND)	Radiographic image, photographic image or clinical measurement were not performed at this time point to evaluate the response of measurable lesions

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[a] Tumor Burden = sum of diameter of target lesions + sum of diameter of up to 10 (maximum 5 per organ) new, measurable lesions. Diameters used:

- For nodal disease, shortest axis
- For non-nodal disease, longest diameters

Table 16. Matrix for Determining the Overall Response at Each Assessment Point

Measurable Response	Non-measurable Response		Overall Response
Target and new, measurable lesions (tumor burden)[a], %	Non-target	New, non-measurable lesions	Using modified irRC-RECIST
↓100[e]	Absent/NA[d]	Absent	iCR[b]
↓100	Present/ND/**iUE**	Any	iPR[b]
↓100	Unequivocal progression	Any	iPR[b]
↓≥ 30	Absent/Present/NA[d]/ND/**iUE**	Any	iPR[b]
↓≥ 30	Unequivocal progression	Any	iPR[b]
↓< 30 to ↑< 20	Absent/Present/NA[d]/ND/**iUE**	Any	iSD
↓< 30 to ↑< 20	Unequivocal progression	Any	iSD
↑≥ 20[f]	Any	Any	iPD[b]
iUE	Any	Any	iUE
ND	Any	Any	iUE
NA[c]	Any	Any	iUE

iCR = complete response (per modified irRC-RECIST); iPR = partial response (per modified irRC-RECIST); iSD = stable disease (per modified irRC-RECIST); iPD = progressive disease (per modified irRC-RECIST); iUE = unevaluable (per modified irRC-RECIST); ND = not done; NA = not applicable.

[a] Decrease disease relative to baseline, including new measurable lesions only (> 10 mm).

[b] iCR or iPR progression should be confirmed by a second, consecutive assessment at least 4 weeks (28 days) apart. Rapid clinical deterioration is an exception for confirming initial iPD.

[c] No target lesions identified at baseline. When a patient has only nonmeasurable disease (ie, no target lesions identified at baseline) the response will be unevaluable.

[d] No non-target lesions identified at baseline.

[e] Disappearance of all non-lymph node lesions and all lymph nodes < 10 mm in short axis would also be iCR even if lymph node measurements prevent 100% tumor burden reduction.

[f] In addition to relative increase of ≥ 20%, the tumor burden must also demonstrate an absolute increase of ≥ 5 mm from nadir for iPD. If the tumor burden does not demonstrate ≥ 5 mm increase from nadir but tumor burden is increased ≥ 20% from the nadir, response should be recorded as iSD.

Determination of best overall response is based on changes in total tumor burden from the baseline (nadir, for iPD) tumor assessment, regardless of any initial increase in baseline lesions or the appearance of new lesions.

Subjects are considered to have iPR or iSD even if new lesions were present, as long as they met the respective thresholds of response as described in Table 16.

A best overall response of iSD requires a visit response of iSD or better no earlier than **84** days after the date of enrollment; otherwise the overall response will be unevaluable (iUE).

Confirmation of Response (iCR or iPR):
To be assigned a status of iCR or iPR changes in tumor measurements must be confirmed by consecutive repeat assessments performed no less than 4 weeks (28 days) after the criteria for response are first met.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of iCR depends on this determination, it is recommended that the residual lesion be investigated (ie, biopsy) to confirm the iCR status.

Confirmation of Disease Progression:
If a subject is classified as having iPD at a post baseline tumor assessment, then confirmation of iPD by a second assessment ≥ 4 weeks (28 days) later in the absence of clinical instability (Section 3.1.3.1) is required. The definition of confirmation of progression represents a ≥ 20% increase in the total tumor burden (ie, the sum of diameters of target lesions plus up to 10 [maximum 5 per organ] new measurable lesions per time point) and absolute increase of ≥ 5 mm in sum of diameters compared to the nadir at two consecutive time points at least 4 weeks (28 days) apart (with the date of progression considered to be the time of the initial evaluation showing iPD).

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of iPD at the time should have the reason for treatment discontinuation classified as “clinically unstable” (Section 3.1.3.1). Every effort should be made to document the objective progression even after discontinuation of treatment.

Subjects who have had a procedure to completely/partially resect a lesion will be evaluated as follows:
The procedure itself and all post-procedure lesion assessments should always be recorded in the CRF. A completely resected lesion should be assigned a default code of 0 mm (for target lesions) or “absent” (for non-target lesions). A partially resected lesion should be assigned its measurement post-procedure (for target lesions) or “present” (for non-target lesions). If the resected lesion contained no melanoma under pathology

evaluation, subsequent tumor assessments post-procedure may be used for tumor burden calculations and/or determination of response. If the resected lesion contained melanoma or pathology results were unknown, the recorded tumor assessments post-procedure may be used for tumor burden calculations, but determination of response will be considered iUE for response except in the case of iPD.

If the new tumor burden post-procedure is lower than the nadir before the procedure, then the new nadir will be set to the post-procedure tumor burden. Otherwise, the previous pre-procedure nadir will be retained as the nadir. Subsequent assessments for iPD will be determined from the nadir.

Merging lesions:

When two or more target/new measurable lesions merge, the smaller lesion should have 0 mm recorded for the current and all future assessments, and the larger lesion should have the longest diameter of the merged lesion recorded for the current assessment and be followed for future assessments. When two or more non-target/new non-measurable lesions merge, the smaller lesion should be recorded as absent for the current and all future assessments, and the larger lesion should be recorded as present for the current assessment and followed for future assessments. If a target/new measurable lesion and a non-target/new non-measurable lesion merge, the non-target/new non-measurable lesion should be absent for the current and all future assessments while the target lesion/new measurable lesion should include both merged lesions for recording measurements. Any lesion with measurement 0 mm that resulted from merging with another lesion(s) should be documented as lesions that were combined with and not truly disapearing lesions.

Separating lesions:

When a target/new measurable lesion splits into 2 or more lesions. The largest measurable part of the split lesion should be considered to be the previously recorded target/new measurable lesion with measurements provided for the current assessment and followed for future assessments. The dimensions of the split parts would still be target/new measurable lesions. When a nontarget/new nonmeasurable lesion splits into 2 or more lesions, the split parts remain nontarget lesions for the duration of the study. For more information, refer to "Follow-up Assessments of Tumor Lesions" in this same appendix. Any new lesions that result from separating should be documented as lesions that were generated by separating and not truly new lesions.

Appendix G. Modifications to Conventional RECIST Guidelines for Assessment of Disease Response in Phase 3

	Conventional RECIST 1.1	Study 20110265 RECIST Modifications
Measurable lesions	○ Non-lymph node longest axis ≥ 10mm (on CT, MRI, or calipers) ○ Non-lymph node longest axis ≥ 20mm (on X-ray) ○ Lymph node short axis ≥ 15mm	○ Target lesions must be measurable on CT or MRI only ○ Lesions not measurable on CT or MRI are considered non-target
Number of target lesions	○ Up to 2 per organ, maximum 5 total	○ Up to 5 per organ, maximum 10 total
Overall Response:		
CR	○ Confirmation of CR or PR is not required for RCTs ○ Disappearance of all lesions, except lymph node short axis < 10 mm	
PR	○ Confirmation of CR or PR not required ○ ≥ 30% reduction in sum of diameters in target lesions	
SD	○ Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD	
PD from target lesions	○ Increase from nadir by ≥ 20% ○ ≥ 5 mm absolute increase above nadir	
PD from non-target lesions	○ Appearance of a new lesion (measurable or not) is a PD	

Amendment 5

Protocol Title: A Phase 1b/3, Multicenter, Trial of Talimogene Laherparepvec in Combination With Pembrolizumab (MK-3475) for Treatment of Unresectable Stage IIIB to IVM1c Melanoma (MASTERKEY-265)

Amgen Protocol Number (Talimogene laherparepvec) 20110265

EudraCT number 2014-000185-22

NCT number 02263508

Amendment Date: 15 January 2020

Rationale:

This protocol is being amended to:

- Update statistical characteristics of the group sequential overall survival (OS) analyses and add in a third interim OS analysis for efficacy planned after 315 events. Based on the updated results from the CHECKMATE-067 trial (Larkin et al, 2019), a delay in the OS treatment effect could be present in the melanoma trial involving combination immunotherapy (ie, nivolumab plus ipilimumab versus nivolumab). To optimize the opportunity to observe statistical significance prior to the OS primary analysis (PA) if there is a late survival effect that would not be achieved at OS interim anlaysis (IA)1 or OS IA2, an additional look at OS IA3 (n = 315) was added prior to the OS PA. The trigger for 315 was selected to achieve approximately half the information gain between n = 282 and n = 346, and is halfway between the expected timings of OS IA2 and OS PA. The protocol is amended to include this additional analysis prior to any formal evaluation of efficacy related to progression free survival or overall survival. Appropriate alpha has been allocated for all of the efficacy analyses.
- Update the background to include the updated OS results from the KEYNOTE-006 and CHECKMATE-067 trials.
- Update exploratory objectives to evaluate PROs as assessed by the EORTC QLQ-C30 and EuroQoL-5D-3L (EQ-5D-3L) subscales and add language for Patient reported outcome (PRO) population assessment.
- An exploratory endpoint of assessing lesion level response was added to explore the systemic effect of talimogene laherparevec at the lesion level.
- Clarify covariates for efficacy in subgroup or multivariate analyses.
- Clarify language for interim efficacy analyses including possible hypotheses tests at planned analyses and operating characteristics of the primary analysis of progression-free survival (PFS) and sequential tests of OS.
- Add text to clarify that in the phase 1b part of the study when nodal disease regresses to below 10 mm, the nodal lesion measurement should be recorded as 0 x 0 mm instead of the actual measurement.

- Clarify that no index lesions identified at baseline (footnote “d”) is associated with “Not applicable (NA)” instead of “Not done (ND) in Table 14 and Table 16. Add “unevaluable (UE) or iUE (unevaluable by modified Immune-related Response Criteria [irRC] simulating Response Evaluation Criteria in Solid Tumors (RECIST) [irRC-RECIST]) for Table 14 or Table 16, respectively” following “ND” for non-measurable response (non-index or non-target).
- Clarify number of days after the date of enrollment for visit response of stable disease by modified irRC-RECIST (iSD) or better.
- Remove retired language for self-evident corrections.
- Administrative, typographical, and formatting changes were made throughout the protocol.

Description of Changes:

Section: Global

Change: Updated version date throughout document from 24 January 2018 to **15 January 2020**

Section: Global

Change: Editorial changes (including typographical, grammatical, and formatting) have been made throughout the document.

Section: Title page

Add:

Date:	01 April 2014
Amendment 1 Date:	15 May 2015
Amendment 2 Date:	25 September 2015
Amendment 3 Date:	12 April 2017
Amendment 4 Date:	24 January 2018
Amendment 5 Date:	**15 January 2020**

This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures.

Section: Protocol Synopsis, Study Design, Phase 3, Paragraph 5

Replace:

The futility analysis based on iORR and iDCR per blinded independent central review using modified irRC-RECIST is planned to include the first 160 subjects (80 per arm) that have been enrolled and have had an opportunity to be followed for the tumor assessment scheduled at week 24. Interim OS analyses are planned at the primary analysis of PFS and after 282 events are observed**.** A non-binding futility analysis of OS will be conducted at the 282 OS event interim analysis if the first and second interim OS analyses do not meet their respective criterion for statistical significance. However, if 282 death events are observed prior to the 407th PFS event, then the first OS interim analysis will occur with 282 events and include a PFS interim analysis with all PFS events. In this case, the second OS interim analysis using all events will be performed at the PFS primary analysis. For more details see Section 10.4.1.4.

With:

The futility analysis based on iORR and iDCR per blinded independent central review using modified irRC-RECIST is planned to include the first 160 subjects (80 per arm) that have been enrolled and have had an opportunity to be followed for the tumor assessment scheduled at week 24. Interim OS analyses are planned at the **time of the** primary analysis of PFS**,** after 282 **OS** events are observed**, and after 315 OS events are observed.** A non-binding futility analysis of OS will be conducted at the 282 OS event interim analysis if the first and second interim OS analyses do not meet their respective criterion for statistical significance. However, if 282 death events are observed prior to the 407th PFS event, then the first OS interim analysis will occur with 282 events and include a PFS interim analysis with all PFS events. In this case, the second OS interim analysis using all events will be performed at the PFS primary analysis. For more details see Section 10.4.1.4.

Section: Protocol Synopsis, Statistical Considerations, Phase 3, Planned method of analyses, Paragraph 4

Replace:

At the time of the PFS primary analysis, an interim efficacy OS analysis will be performed. A second interim OS analysis is planned after 282 events for efficacy and futility. The interim OS futility analysis will be non-binding and define futility as a conditional power < 10% assuming a constant treatment effect; however, futility will also be similarly defined by considering a possible non-constant treatment effect that increases over time. The order for the event-driven OS interim and PFS primary analyses may not be as anticipated due to incorrect design assumptions. If 282 OS events are observed prior to 407 PFS events, the first event-driven analysis will be an OS interim with 282 OS events and a PFS interim using all events.

With:

At the time of the PFS primary analysis, an interim efficacy OS analysis will be performed. **The** second interim OS analysis is planned after 282 events for efficacy and futility. The interim OS futility analysis will be non-binding and define futility as a conditional power < 10% assuming a constant treatment effect; however, futility will also be similarly defined by considering a possible non-constant treatment effect that increases over time. The order for the event-driven OS interim and PFS primary analyses may not be as anticipated due to incorrect design assumptions. If 282 OS events are observed prior to 407 PFS events, the first event-driven analysis will be an

OS interim with 282 OS events and a PFS interim using all events. **The third interim OS analysis for efficacy is planned after 315 events are observed.**

Section: Study Glossary (new)

Add:

mOS	**median overall survival**

Section: 1.3, Exploratory, Phase 3, bullet 9 (new)

Add:

- **To evaluate the response rates (partial, complete, partial or complete) and maximum decrease in lesion size, separately for visceral, injected, and uninjected non-visceral lesions.**

Section: 2.1, Melanoma and Programmed Cell Death 1 (PD-1) Receptor Inhibitor, Paragraph 3

Replace:

It has been postulated that antibodies that block the interaction between PD-1 and PD-L1 in tumors may preferentially release the cytotoxic function of tumor-specific T cells with fewer systemic toxic effects than those that are seen with other immune checkpoint inhibitors (Pardoll, 2012; Ribas; 2012; Okazaki and Honjo, 2007). Inhibitory antibodies targeted to PD-1 and PD-L1 have demonstrated objective responses in multiple tumor types including melanoma (Robert et al, 2015; Hamid et al, 2013; Brahmer et al, 2012; Topalian et al, 2012). The combination of PD-1 blockade with nivolumab and CTLA-4 blockade with ipilimumab has resulted in longer progression free survival than either agent alone but was associated with a high rate of grade 3 or 4 adverse events (Larkin et al, 2015).

With:

It has been postulated that antibodies that block the interaction between PD-1 and PD-L1 in tumors may preferentially release the cytotoxic function of tumor-specific T cells with fewer systemic toxic effects than those that are seen with other immune checkpoint inhibitors (Pardoll, 2012; Ribas; 2012; Okazaki and Honjo, 2007). Inhibitory antibodies targeted to PD-1 and PD-L1 have demonstrated objective responses in multiple tumor types including melanoma (Robert et al, 2015; Hamid et al, 2013; Brahmer et al, 2012; Topalian et al, 2012). **Anti-PD-1 antibodies have also been shown to improve overall survival in melanoma (Larkin et al, 2019; Robert et al, 2019).** The combination of PD-1 blockade with nivolumab and CTLA-4

blockade with ipilimumab has resulted in **significantly** longer progression free survival **and overall survival** than **ipilimumab** but was associated with a high rate of grade 3 or 4 adverse events (**Larkin et al, 2019;** Larkin et al, 2015).

Section: 2.3, Pembrolizumab Background, Paragraph 2

Replace:

A phase 3 registration trial (KEYNOTE-006) of pembrolizumab versus ipilimumab in ipilimumab-naive subjects with advanced melanoma has been published (clinicaltrials.gov identifier NCT01866319, Schachter et al, 2007). This is a 3-arm study to evaluate the safety and efficacy of two dosing schedules of pembrolizumab compared to ipilimumab for the treatment of ipilimumab-naïve participants with unresectable or metastatic melanoma. Subjects are randomized 1:1:1 to receive pembrolizumab 10 mg/kg every 2 weeks for up to 2 years or pembrolizumab 10 mg/kg every 3 weeks for up to 2 years or ipilimumab 3 mg/kg for a total of 4 doses. Primary endpoints of this study are progression free survival (PFS) and overall survival (OS). At an interim analysis with 834 subjects enrolled and median duration of follow-up 7.9 months (range 6.1-11.5 months), the response rate for pembrolizumab every 2 weeks was 33.7% and every 3 weeks was 32.9% as compared with ipilimumab at 11.9% ($p < 0.001$ for both comparisons) (Robert et al, 2015). The PFS hazard ratio was 0.58 ($P < 0.001$ for both pembrolizumab regimens versus ipilimumab), and the hazard ratio for death for pembrolizumab every 2 weeks was 0.63 ($P = 0.0005$) and 0.69 for pemrbolizumab every 3 weeks ($P = 0.0036$) versus ipilimumab. Rates of treatment-related adverse events of grade 3 to 5 were lower in the pembrolizumab groups (13.3% and 10.1%) than in the ipilimumab group (19.9%) (Robert et al, 2015).

With:

A phase 3 registration trial (KEYNOTE-006) of pembrolizumab versus ipilimumab in ipilimumab-naive subjects with advanced melanoma has been published (clinicaltrials.gov identifier NCT01866319, Schachter et al, 2007). This is a 3-arm study to evaluate the safety and efficacy of two dosing schedules of pembrolizumab compared to ipilimumab for the treatment of ipilimumab-naïve participants with unresectable or metastatic melanoma. Subjects are randomized 1:1:1 to receive pembrolizumab 10 mg/kg every 2 weeks for up to 2 years or pembrolizumab 10 mg/kg every 3 weeks for up to 2 years or ipilimumab 3 mg/kg for a total of 4 doses. Primary endpoints of this study are progression free survival (PFS) and overall survival (OS). At an interim analysis with 834 subjects enrolled and median duration of follow-up 7.9 months (range

6.1-11.5 months), the response rate for pembrolizumab every 2 weeks was 33.7% and every 3 weeks was 32.9% as compared with ipilimumab at 11.9% ($p < 0.001$ for both comparisons) (Robert et al, 2015). The PFS hazard ratio was 0.58 ($P < 0.001$ for both pembrolizumab regimens versus ipilimumab), and the hazard ratio for death for pembrolizumab every 2 weeks was 0.63 ($P = 0.0005$) and 0.69 for pembrolizumab every 3 weeks ($P = 0.0036$) versus ipilimumab. Rates of treatment-related adverse events of grade 3 to 5 were lower in the pembrolizumab groups (13.3% and 10.1%) than in the ipilimumab group (19.9%) (Robert et al, 2015). **The overall survival benefit of pembrolizumab versus ipilimumab continued to hold after a median follow-up of 57.7 months (range 56.7 to 59.2 months). The median overall survival (mOS) was 32.7 months in the combined pembrolizumab groups and 15.9 months in the ipilimumab group (hazard ratio = 0.73, 95% confidence interval of 0.61 to 0.88, P = 0.00049) (Robert et al, 2019).**

Section: 2.4, Rationale for Combination Therapy of Talimogene Laherparepvec and Pembrolizumab, Paragraph 2

Replace:

A prior concurrent regimen of nivolumab, a PD-1 inhibitor, with ipilimumab, a CTLA-4 inhibitor has yielded higher response rates (57.5%, 95% CI 52.0 to 63.2) and median progression free survival (11.5 months, 95% CI 8.9 to 16.7) in advanced melanoma than either agent as monotherapy (Larkin et al, 2015), suggesting that immune therapies can be given concurrently to improve efficacy. However, toxicity was also increased with 55% having grade 3 or 4 adverse events for combination versus 16.3% for nivolumab and 27.3% for ipilimumab. As both pembrolizumab and talimogene laherparepvec have had relatively low toxicity as single agents, it is possible that the overall incidence of severe adverse events would remain low when they are combined as has been seen with the talimogene laherparepvec and ipilimumab combination.

With:

A prior concurrent regimen of nivolumab, a PD-1 inhibitor, with ipilimumab, a CTLA-4 inhibitor has yielded higher response rates (57.5%, 95% CI 52.0 to 63.2) and median progression free survival (11.5 months, 95% CI 8.9 to 16.7) in advanced melanoma than **ipilimumab** (Larkin et al, 2015)**. Updated results also showed a longer mOS for the combination (mOS > 60 months) versus ipilimumab (mOS = 19.9 months) (Larkin et al, 2019),** suggesting that immune therapies can be given concurrently to improve efficacy. However, toxicity was also increased with 55% having grade 3 or

4 adverse events for combination versus 16.3% for nivolumab and 27.3% for ipilimumab. As both pembrolizumab and talimogene laherparepvec have had relatively low toxicity as single agents, it is possible that the overall incidence of severe adverse events would remain low when they are combined as has been seen with the talimogene laherparepvec and ipilimumab combination.

Section: 3.1.2, Phase 3 Study Design, Paragraph 7

Replace:

Additional interim safety analyses may be performed if warranted based on results from the planned safety and/or interim analyses or if requested by the clinical study team or the DMC. The futility analysis based on iORR and iDCR using modified irRC-RECIST per blinded independent central review is planned to include the first 160 subjects (80 per arm) that have been enrolled and have had an opportunity to be followed for the tumor assessment scheduled at week 24. This futility analysis will be based on Bayesian methods. The talimogene laherparepvec plus pembrolizumab arm is considered to be futile if the posterior probability that at least 6% absolute increase for iORR (at least 10% for iDCR) from the pembrolizumab is < 0.65 (< 0.75 for iDCR). A DMC will be responsible to review interim safety and non-binding futility analyses for iORR and iDCR. The DMC is also responsible to review the results from the primary analysis of PFS by blinded independent central review using modified RECIST 1.1 and all interim OS analyses performed by an external independent biostatistics group. At the time of PFS primary analysis, an interim OS efficacy analysis will be performed by the external biostatistics group and reviewed by the DMC. A second interim OS analysis is planned after 282 events have occurred. If OS is not declared statistically significant at the second interim analysis, a non-binding futility analysis will be performed. However, if 282 OS events are observed prior to the event goal for the primary PFS, then the first OS interim will be the event-driven (ie, 282 events) and a PFS interim will be conducted with all PFS events at the time of the 282 OS events interim analysis. In this case, the second OS interim analysis will be performed at the PFS primary analysis with all OS events. Refer to Section 10.4.1.4 for additional information.

With:

Additional interim safety analyses may be performed if warranted based on results from the planned safety and/or interim analyses or if requested by the clinical study team or the DMC. The futility analysis based on iORR and iDCR using modified irRC-RECIST per blinded independent central review is planned to include the first 160 subjects

(80 per arm) that have been enrolled and have had an opportunity to be followed for the tumor assessment scheduled at week 24. This futility analysis will be based on Bayesian methods. The talimogene laherparepvec plus pembrolizumab arm is considered to be futile if the posterior probability that at least 6% absolute increase for iORR (at least 10% for iDCR) from the pembrolizumab is < 0.65 (< 0.75 for iDCR). A DMC will be responsible to review interim safety and non-binding futility analyses for iORR and iDCR. The DMC is also responsible to review the results from the primary analysis of PFS by blinded independent central review using modified RECIST 1.1 and all interim OS analyses performed by an external independent biostatistics group. At the time of PFS primary analysis, an interim OS efficacy analysis will be performed by the external biostatistics group and reviewed by the DMC. **The** second interim OS analysis is planned after 282 events have occurred. If OS is not declared statistically significant at the second interim analysis, a non-binding futility analysis will be performed. However, if 282 OS events are observed prior to the event goal for the primary PFS, then the first OS interim will be the event-driven (ie, 282 events) and a PFS interim will be conducted with all PFS events at the time of the 282 OS events interim analysis. In this case, the second OS interim analysis will be performed at the PFS primary analysis with all OS events. **The third interim OS analysis for efficacy is planned after 315 events have occurred.** Refer to Section 10.4.1.4 for additional information.

Section: 3.5.2, End of Study, Primary Completion, Paragraph 1
Delete:

Primary Completion: The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s)~~, for the purposes of conducting the primary analysis,~~ whether the ~~study concluded as planned in the protocol or was terminated early~~.

Section: 3.5.2, End of Study, Primary Completion, Paragraph 2
Add:

The primary completion date is the date when data for the primary endpoint**(s)** are last collected for the purpose of conducting the primary analysis.

Section: 4.1.1.1, Inclusion Criteria for Phase 1b and Phase 3, Criterion #104

Add:

Disease stage **defined as one of the following (per the seventh edition of the American Joint Committee on Cancer [AJCC] Cancer Staging Manual)**: Subject with unresectable stage IIIB, IIIC, IVM1a, IVM1b, or IVM1c melanoma

Section: 7.1, Schedule of Assessments, Table 6, footnote "r"

Replace:

[r] Blood for PK of pembrolizumab: Pre-dose trough will be collected at week 0 (ie, pembrolizumab cycle 1), week 3 (ie, pembrolizumab cycle 2), week 12 (ie, pembrolizumab cycle 5), week 27 (ie, pembrolizumab cycle 9), week 39 (ie, pembrolizumab cycle 13) every 12 weeks (4 cycles) thereafter, at safety follow-up visit (30 [+7] days after discontinuation of study treatment), and again 3 months after study discontinuation or up until the subject starts new anticancer therapy, whichever occurs first. Every effort should be taken to collect samples at 30 days and 3 months after end of pembrolizumab treatment. All trough samples should be drawn within 24 hours before infusion of pembrolizumab. Pembrolizumab PK sample collection and analyses in phase 3 may be discontinued if ongoing PK results from this study continue to be consistent with existing PK data from other pembrolizumab melanoma clinical trials.

With:

r Blood for PK of pembrolizumab: Pre-dose trough and post-dose peak PK samples will be collected at week 0 (ie, pembrolizumab cycle 1). Pre-dose trough samples only will be collected on day 1 of week 3 (ie, pembrolizumab cycle 2), week 12 (ie, pembrolizumab cycle 5), week 27 (ie, pembrolizumab cycle 9), week 39 (ie, pembrolizumab cycle 13) every 12 weeks (4 cycles) thereafter, at safety follow-up visit (30 [+7] days after discontinuation of study treatment), and again 3 months after study discontinuation or up until the subject starts new anticancer therapy, whichever occurs first. Every effort should be taken to collect samples at 30 days and 3 months after end of pembrolizumab treatment. All trough samples should be drawn within 24 hours before infusion of pembrolizumab. The peak sample should be drawn within 30 minutes after the end of the infusion. Pembrolizumab PK sample collection and analyses in phase 3 may be discontinued if ongoing PK results from this study continue to be consistent with existing PK data from other pembrolizumab melanoma clinical trials.

Section: 10.1.1.3, Exploratory Endpoints, bullet 5

Replace:

- HSU estimates derived via EQ-5D-3L at each assessment in phase 3 and post-progression.

With:

- **Changes in** HSU estimates derived via EQ-5D-3L

Section: 10.1.1.3, Exploratory Endpoints, bullet 11 (new)

Add:

- **Response rates (partial, complete, partial or complete) and maximum decrease in lesion size, separately for visceral, injected, and uninjected non-visceral lesions.**

Section: 10.1.2, Analysis Sets, PRO Population

Replace:

PRO Analysis Sets

PRO analysis set will include subset of subjects in the Full Analysis Set who had received at least one dose of study therapy and had at least one PRO assessment.

With:

PRO **Population**

The PRO population includes the subset of the subjects in the full analysis set who had received at least 1 dose of study therapy and had at least 1 PRO assessment. A PRO assessment will be defined as completed if at least 1 subscale/domain can be calculated from the questionnaire. Patient reported outcome populations will be defined separately for each questionnaire (EORTC QLQ-C30 and EQ-5D-3L) and for the secondary endpoint of EORTC QLQ-C30 GHS/QoL.

Section: 10.1.3, Covariates and Subgroups, Paragraph 2

Delete:

The following baseline covariates and randomization stratification factors may be used to examine ~~all~~ efficacy in subgroups or in multivariate analyses:

Section: 10.1.3, Covariates and Subgroups, Paragraph 2, bullets 10, 11, and 14

Replace:

- The sum of longest, or shortest for nodal, diameters of target lesions (SLD)
- Pre-randomization PD-L1 status (positive, negative, indeterminant/unknown)
- Pre-randomization of $BRAF^{V600}$ mutation: yes vs no

With:

- The sum of longest, or shortest for nodal, diameters of target lesions (SLD) **determined by blinded independent central review (will be dichotomized based on median)**
- **Baseline** PD-L1 status (positive **vs not positive**)
- **Baseline** of $BRAF^{V600}$ mutation: yes vs no **vs missing/unknown**

Section: 10.2.2, Sample Size Considerations for Phase 3, Paragraph 2

Replace:

The overall Type I error for the dual primary endpoints is 2-sided 0.05. The event goal for PFS to achieve 90% power at 2-sided 0.005 is 407 and that for OS to achieve 90% power at a 2-sided 0.045 is 346 after taking into account the group sequential interim OS analyses. The OS event goal is not adjusted for the non-binding OS futility assessment at the second OS interim analysis. The sample size is 660 (ie, 330 per arm) based on an estimate of 346 death events occurring within 5 years (60 months) with approximately 48% of subjects censored. Assuming a non-uniform subject accrual rate for which 50% of cumulative enrollment is accrued at 2/3 of expected total enrollment period (Lachin and Foulkes, 1986), and exponential distributions for loss to follow up for PFS and OS with an annual rate of 5% for OS and 10% for PFS, Table 9 displays estimated timing of analysis based on 2 scenarios of enrollment rates:

With:

The overall Type I error for the dual primary endpoints is 2-sided 0.05. The event goal for PFS to achieve 90% power at 2-sided 0.005 is 407 and that for OS to achieve 90% power at a 2-sided 0.045 is 346 after taking into account the group-sequential interim OS analyses. The OS event goal is not adjusted for the non-binding OS futility assessment at the second OS interim analysis. The sample size is 660 (ie, 330 per arm) based on an estimate of 346 death events occurring within 5 years (60 months) with approximately 48% of subjects censored. Assuming a non-uniform subject accrual rate for which 50% of cumulative enrollment is accrued at 2/3 of expected total enrollment period (Lachin and Foulkes, 1986), and exponential distributions for loss to follow up for PFS

and OS with an annual rate of 5% for OS and 10% for PFS, Table 9 displays estimated timing of analysis based on **the actual** enrollment rate:

Section: 10.2.2, Sample Size Considerations for Phase 3, Table 9

Replace:

Table 9. Timing of Primary Analysis for PFS (at 407 events) and OS (at 346 events)

Average Enrollment Rate	Enrollment Duration (month)	PFS PA DCO (month)	OS Events (% event goal) at PFS PA DCO	OS PA DCO (month)
20/month	33	44	240 (69%)	62
33/month	20	33	222 (64%)	53

DCO = data cutoff at event goal; OS = overall survival; PA = primary analysis; PFS_1 = progression free survival per blinded independent central review using modified RECIST 1.1. N = 660

With:

Table 9. Timing of Primary Analysis for PFS (at 407 events) and OS (at 346 events)

Enrollment Duration (month)	PFS PA DCO (month)	OS Events (% event goal) at PFS PA DCO	OS PA DCO (month)
26	**48**	**252** (**73**%)	**75**

DCO = data cutoff at event goal; OS = overall survival; PA = primary analysis; PFS_1 = progression free survival per blinded independent central review using modified RECIST 1.1.

[redacted]

Section: 10.2.2, Sample Size Considerations for Phase 3, Table 10, footnote a

Add:

[redacted]

Section: 10.4.1.4, Interim Efficacy and Futility Analysis (Phase 3), Paragraphs 1 and 2

Replace:

There are 4 planned analysis time points for hypothesis testing, including primary and/or interim analyses of the 5 hypotheses (H): H_1, associated with OS; H_2, PFS by blinded independent central review assessed modified RECIST 1.1; H_3, iPFS by blinded independent central review assessed modified irRC-RECIST; H_4, iCRR by blinded independent central review assessed modified irRC-RECIST; and H_5, OS subgroup

excluding IVM1c (Table 10). The analysis times are defined by the following event-driven time points with the DMC responsible for Analyses #1 and #2.

1. PFS primary analysis at 407 events (DMC).
2. OS interim analysis at 282 events (including a futility analysis) (DMC).
3. OS primary analysis at 346 events.
4. OS subgroup primary analysis at earlier of 208 events in subgroup or 5 years minimum follow-up.

Note that there is no sequential order in these 4 analysis times (with the exception that Analysis #2 is before Analysis #3). Each analysis time may also include interim or primary analyses for the other endpoints. Endpoints to be analyzed, and the type of analysis (ie, interim or primary), are presented in Table 11 and are dependent on which hypotheses have been rejected. For example, testing for iCRR and iPFS at an analysis time point will be conditional upon previously rejecting either H_1 or H_2. O'Brien-Fleming group sequential boundaries based on the Lan-DeMets approach (O'Brien and Fleming, 1979) will be used for testing endpoints with interim analyses. Multiple testing procedures will utilize the graphic-based Maurer-Bretz approach (Section 10.5).

With:

There are **5** planned analysis time points for hypothesis testing, including primary and/or interim analyses of the 5 hypotheses (H): H_1, associated with OS; H_2, PFS by blinded independent central review assessed modified RECIST 1.1; H_3, iPFS by blinded independent central review assessed modified irRC-RECIST; H_4, iCRR by blinded independent central review assessed modified irRC-RECIST; and H_5, OS subgroup excluding IVM1c (Table 10). The analysis times are defined by the following event-driven time points with the DMC responsible for Analyses #1**,** #2**, and #3**.

1. **OS interim analysis and** PFS primary analysis at 407 **PFS** events (DMC).
2. OS interim analysis at 282 events (including a futility analysis) (DMC).
3. **OS interim analysis at 315 events (DMC).**
4. OS primary analysis at 346 events.
5. OS subgroup primary analysis at earlier of 208 events in subgroup or 5 years minimum follow-up.

Note that there is no sequential order in these **5** analysis times (with the exception that Analysis #2 is before Analysis #3**, and Analysis #3 before Analysis #4**). Each analysis time may also include interim or primary analyses for the other endpoints. Endpoints to

be analyzed, and the type of analysis (ie, interim or primary), are presented in Table 11 and are dependent on which hypotheses have been rejected. For example, testing for iCRR and iPFS at an analysis time point will be conditional upon previously rejecting either H_1 or H_2. O'Brien-Fleming group sequential boundaries based on the Lan-DeMets approach (O'Brien and Fleming, 1979) will be used for testing endpoints with interim analyses. Multiple testing procedures will utilize the graphic-based Maurer-Bretz approach (Section 10.5).

Section: 10.4.1.4, Interim Efficacy and Futility Analysis (Phase 3), Paragraph 3, bullets 3, 6, and 7

Replace:

3. At each of the 4 planned analysis times, it will be considered an interim analysis of iCRR and iPFS, rather than the primary analysis, if the maximum information has not been reached for the respective endpoint at that time. For example, if H_3 is tested in an analysis that includes fewer than 256 iPFS events, then it will be an interim analysis of iPFS that includes all observed events; otherwise, it will be the primary analysis with all iPFS times censored after the date of the 256th event. If all randomized subjects do not have at least 36 weeks follow-up in an analysis, then it will be an interim analysis for iCRR only including those subjects with at least 36 weeks follow-up; otherwise, it will be the primary analysis and include all randomized subjects. With the exception of PFS, the hypothesis for an endpoint may be re-tested after its primary analysis using its primary analysis data if alpha is subsequently propagated to it from the rejection of another hypothesis.
6. The OS hypothesis (H_1) will be tested at Analyses #1-3 with all (Analysis #1) or required number (Analysis #2 and Analysis #3) of events in the absence of its prior rejection (or futility at Analysis #2).
7. The OS subgroup hypothesis (H_5) will be tested at the first and all subsequent analysis times when alpha can be propogated to it from the rejection of H_1 or H_2 followed by H_3 and/or H_4. All OS events in the subgroup at the end of 5 years follow-up will be used if 208 events have not been observed. If H_1 is not rejected by Analysis #3, it will be tested again using events at Analysis #3 if alpha can be propogated from the rejection of H_5 at Analysis #4.

With:

3. At each of the **5** planned analysis times, it will be considered an interim analysis of iCRR and iPFS, rather than the primary analysis, if the maximum information has not been reached for the respective endpoint at that time. For example, if H_3 is tested in an analysis that includes fewer than 256 iPFS events, then it will be an interim analysis of iPFS that includes all observed events; otherwise, it will be the primary analysis with all iPFS times censored after the date of the 256th event. If all randomized subjects do not have at least 36 weeks follow-up in an analysis, then it will be an interim analysis for iCRR only including those subjects with at least 36 weeks follow-up; otherwise, it will be the primary analysis and include all randomized subjects. With the exception of PFS, the hypothesis for an endpoint may be re-tested after its primary analysis using its primary analysis data if alpha is subsequently propagated to it from the rejection of another hypothesis.

6. The OS hypothesis (H_1) will be tested at Analyses #1-**4** with all (Analysis #1) or required number (Analysis #2**,** Analysis #3**, and Analysis #4**) of events in the absence of its prior rejection (or futility at Analysis #2).
7. The OS subgroup hypothesis (H_5) will be tested at the first and all subsequent analysis times when alpha can be propogated to it from the rejection of H_1 or H_2 followed by H_3 and/or H_4. All OS events in the subgroup at the end of 5 years follow-up will be used if 208 events have not been observed. If H_1 is not rejected by Analysis #**4**, it will be tested again using events at Analysis #**4** if alpha can be propogated from the rejection of H_5 at Analysis #**5.**

Section: 10.4.1.4, Interim Efficacy and Futility Analysis (Phase 3), Paragraph 4 and Table 11

Replace:

Table 11 illustrates possible hypothesis tests at the 4 planned analyses.

Table 11. Study Analyses and Possible Hypothesis Tests

		Hypothesis Tested (Analysis Type)				
Analysis	Timing	H_1 (OS)	H_2 (PFS)	H_3 (iPFS)	H_4 (iCRR)	H_5 (OS subgroup)
#1	407 PFS events	(IA)	(PA)	If reject H_1 or H_2 (IA if < 256 events)	If reject H_1 or H_2 (IA if includes fewer than all randomized)	If reject H_2 and either H_3 or H_4, or reject H_1 and either H_3 or H_4 (IA if < 208 events)
#2	282 OS events	(IA)	n/a (IA if Analysis #2 is performed first)	If reject H_1 or H_2 (PA on first 256 events)	If reject H_1 or H_2 (PA if includes all random-ized)	If reject H_2 and either H_3 or H_4, or reject H_1 and either H_3 or H_4 (IA if < 208 events)
#3	346 OS events	(PA)	n/a	See Analysis #2 above	See Analysis #2 above	See Analysis #2 above
#4	Earlier of 208 OS events in subgroup or 5 years minimum follow-up	If reject H_2 previously and H_5 (PA at first 346 events)	n/a	See Analysis #2 above	See Analysis #2 above	See Analysis #2 above (PA)

With:

Table 11 illustrates possible hypothesis tests at the **5** planned analyses.

Table 11. Study Analyses and Possible Hypothesis Tests

		Hypothesis Tested (Analysis Type)				
Analysis	Timing	H_1 (OS)	H_2 (PFS)	H_3 (iPFS)	H_4 (iCRR)	H_5 (OS subgroup)
#1	407 PFS events	(IA)	(PA)	If reject H_1 or H_2 (IA if < 256 events)	If reject H_1 or H_2 (IA if includes fewer than all random-ized)	If reject H_2 and either H_3 or H_4, or reject H_1 and either H_3 or H_4 (IA if < 208 events)
#2	282 OS events	(IA)	n/a (IA if Analysis #2 is performed first)	If reject H_1 or H_2 (PA on first 256 events)	If reject H_1 or H_2 (PA if includes all random-ized)	If reject H_2 and either H_3 or H_4, or reject H_1 and either H_3 or H_4 (IA if < 208 events)
#3	**315 OS events**	**(IA)**	**n/a**	**If reject H_1 or H_2 (PA on first 256 events)**	**If reject H_1 or H_2 (PA if includes all randomized)**	**If reject H_2 and either H_3 or H_4, or reject H_1 and either H_3 or H_4 (IA if < 208 events)**
#4	346 OS events	(PA)	n/a	See Analysis #2 **and #3** above	See Analysis #2 **and #3** above	See Analysis #2 **and #3** above
#5	Earlier of 208 OS events in subgroup or 5 years minimum follow-up	If reject H_2 previously and H_5 (PA at first 346 events)	n/a	See Analysis #2 **and #3** above	See Analysis #2 **and #3** above	See Analysis #2 **and #3** above (PA)

Section: 10.4.1.4, Futility Analysis for OS

Delete:

At the 282 OS events interim analysis (ie, Analysis #2), if hypothesis H1 is not rejected, then an OS futility analysis will be evaluated by the DMC. The interim OS futility analysis will be non binding and define futility as a conditional power < 10% assuming a constant treatment effect (Denne, 2001); the corresponding OS futility boundary is 0.89, assuming a constant HR = 0.70. OS futility will also be evaluated by the DMC considering a possible non constant treatment effect that increases over time (eg, a 2 interval model with a cutpoint between 4 8 months and constant treatment effect in each interval, where the second interval has a larger effect than the first one). To limit the probability of futility < 0.02, the futility boundary for the observed HR at 282 OS events analysis will be 0.93. Guidelines for this possible late effect will be provided in the DMC charter amendment. Operating characteristics of the primary analysis of PFS and sequential tests of OS are shown in Table 12 based on the OS events expected at Analysis #1~~ based on 2 enrollment scenarios shown in Table 9~~.

Section: 10.4.1, Futility Analysis for OS, Table 12

Replace:

Table 12 Analysis Timing, Nominal Significance Levels, and Boundary Properties by Average Enrollment

Average enrollment	Analysis	Data cut-off (mon)	Endpoint (scenario)	Event (% goal)	Efficacy nominal 2-sided α	Futile HR [b]	Prob. Futile [b]		Efficacy HR	Power total
							H_0	H_1		
20/month	PFS PA	44	PFS	407 (100)	0.0050				0.76	90%
	OS IA_1	44	OS (PFS-)	240 (69)[a]	0.0123				0.72	60%
			OS (PFS+)		0.0143				0.73	62%
	OS IA_2	50	OS (PFS-)	282 (82)	0.0194	0.89	84%	2%	0.76	76%
			OS (PFS+)		0.0219	0.89	83%	2%	0.76	77%
	OS PA	62	OS (PFS-)	346 (100)	0.0376				0.80	90%
			OS (PFS+)		0.0416				0.80	91%
33/month	PFS PA	33	PFS	407 (100)	0.0050				0.76	90%
	OS IA_1	33	OS (PFS-)	222 (64)[a]	0.0088				0.70	52%
			OS (PFS+)		0.0103				0.71	54%
	OS IA_2	41	OS (PFS-)	282 (82)	0.0203	0.89	84%	2%	0.76	76%
			OS (PFS+)		0.0230	0.89	83%	2%	0.76	77%
	OS PA	53	OS (PFS-)	346 (100)	0.0377				0.80	90%
			OS (PFS+)		0.0417				0.80	91%

N = 660

IA = interim analysis; H_0 = null hypothesis; H_1 = alternative hypothesis; HR = hazard ratio; OS = overall survival; PFS = progression free survival; PA = primary analysis.

O'Brien-Fleming spending α for OS; futility if conditional power < 10%; H_0: HR = 1 and H_1: HR = 0.67 (PFS) and 0.70 (OS). Testing OS at an overall 2-sided 0.045 if PFS is not significant at 2-sided 0.005 (eg, PFS-); testing OS at 0.05 when all other null hypotheses are rejected (eg, PFS+).

With:

Table 12 Analysis Timing, Nominal Significance Levels, and Boundary Properties

Analysis	Data cut-off (mon)	Endpoint (scenario)	Event (% goal)	Efficacy nominal 2-sided α	Futile HR [b]	Prob. Futile [b] H_0	Prob. Futile [b] H_1	Efficacy HR	Power total
PFS PA	**48**	PFS	407 (100)	0.0050				0.76	90%
OS IA_1	**48**	OS (PFS-)	**252** (**73**)[a]	0.**0150**				0.**74**	**66**%
		OS (PFS+)		0.**0173**				0.**74**	**67**%
OS IA_2	**52**	OS (PFS-)	282 (82)	0.**0187**	0.89	84%	2%	0.76	76%
		OS (PFS+)		0.**0212**	0.89	83%	2%	0.76	77%
OS IA_3	**61**	**OS (PFS-)**	**315 (91)**	**0.0261**				**0.78**	**84%**
		OS (PFS+)		**0.0292**				**0.78**	**85%**
OS PA	**75**	OS (PFS-)	346 (100)	0.**0336**				0.80	90%
		OS (PFS+)		0.**0372**				0.80	**90**%

IA = interim analysis; H_0 = null hypothesis; H_1 = alternative hypothesis; HR = hazard ratio; OS = overall survival; PFS = progression free survival; PA = primary analysis. O'Brien-Fleming spending α for OS; futility if conditional power < 10%; H_0: HR = 1 and H_1: HR = 0.67 (PFS) and 0.70 (OS). Testing OS at an overall 2-sided 0.045 if PFS is not significant at 2-sided 0.005 (eg, PFS-); testing OS at 0.05 when all other null hypotheses are rejected (eg, PFS+). [redacted]

Section: 10.5.5, Patient Reported Outcome Endpoints and Analyses

Replace:

10.5.5 PRO Endpoints

The PRO analyses will be conducted for subjects in the PRO Analysis Sets. Summary scores at each assessment and changes from baseline of PROs as assessed by EQ-5D-3L and the QLQ-C30 questionnaires will be reported. Changes from baseline will be summarized and at specified time points of interest, differences between treatment groups for each defined score will be analyzed. For the EORTC QLQ-C30 questionnaire, each of the 5 functional scales, 9 symptom scales, and a GHS/QoL subscale (secondary endpoint) will be summarized similarly. The calculation of scores and methods for handling missing data will be based on the questionnaire's standard scoring guidelines. Details of all the PRO analyses will be provided in the statistical analysis plan.

With:

10.5.5 **Patient Reported Outcome** Endpoints **and Analyses**

The PRO analyses will be conducted for subjects in the PRO **population**. Summary scores at each assessment and changes from baseline of PROs as assessed by EQ-5D-3L and the QLQ-C30 questionnaires will be reported. Changes from baseline will be summarized and at specified time points of interest, differences between treatment groups for each defined score will be analyzed. For the EORTC QLQ-C30 questionnaire, each of the 5 functional scales, 9 symptom scales, and a GHS/QoL subscale (secondary endpoint) will be summarized similarly. **For the EQ-5D-3L questionnaire, 2 scores will be estimated: the utility score calculated from the 5 domains using a scoring algorithm, and the VAS score based on the 0 to 100 feeling thermometer.** Details of all the PRO analyses will be provided in the **PRO supplemental** statistical analysis plan.

Section: 12.3, Study Monitoring and Data Collection, Paragraph 6

Delete:

~~Amgen (or designee) will perform self-evident corrections to obvious data errors in the clinical trial database, as documented in the Study Specific Self Evident Corrections Plan. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data (eg, same results sent twice with the same date with different visit week 4 and early termination) and clarifying "other, specify" if~~

~~data are provided (eg, race, physical examination). Each investigative site will be provided a list of the types of corrections applied to study data at the initiation of the trial and at study closeout.~~

Section: 13, References

Add:

Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med*. 2019;381(16):1535-1546.

Robert C, Ribas A, Schachter J, et al. Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-066): post-doc 5-year results from an open-label, multicenter, randomised, controlled, phase 3 study. *Lancet Oncol*. 2019;20(9):1239-1251.

Section: 14, Appendix C, Pregnancy and Lactation Notification Worksheets

Replace:

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: 20110265

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:** _____

Effective Date: March 27, 2011 Page 1 of 1

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: 20110265

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:** _____

Effective Date: 03 April 2012, version 2. Page 1 of 1

With:

Amgen Proprietary - Confidential

AMGEN® Pregnancy Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20110265

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 age (at onset):** ____(in years)

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 last menstrual period (LMP) mm_____/ dd_____/ yyyy_____ ☐Unknown ☐ N/A

Estimated date of delivery mm_____/ dd_____/ yyyy_____

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:** _____

FORM-115199 Version 1.0 Effective Date: 24-Sept-2018

AMGEN® Lactation Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20110265

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 age (at onset):**____(in years)

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:** _____

FORM-115201 Version 1.0 Effective Date: 24-Sept-2018

Section: 14, Appendix D, Modified Immune-related Response Criteria (irRC) for Review of Disease Response in Phase 1b, Follow-up, Paragraph 1

Replace:

At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions (accurately and serially measured in at least 2 dimensions and for which the longest diameter is ≥ 5 mm) are added together to provide the total tumor burden.

With:

At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions (accurately and serially measured in at least 2 dimensions and for which the longest diameter is ≥ **10** mm) are added together to provide the total tumor burden.

Section: 14, Appendix D, Modified Immune-related Response Criteria (irRC) for Review of Disease Response in Phase 1b, Follow-up, Paragraph 3

Add:

For index and new measurable nodal lesions < 10 mm, the measurement should be recorded as the 0 x 0 mm instead of the actual measurement.

Section: 14, Appendix D, Modified Immune-related Response Criteria (irRC) for Review of Disease Response in Phase 1b, Evaluation of Objective Response Rate:, Table 14

Replace:

Measurable Response	Non-measurable Response		Overall Response
Index and new, measurable lesions (tumor burden)[a], %	Non-index	New, non-measurable lesions	Using irRC
↓100	Absent/NA[d]	Absent	CR[b]
↓100	Present/ND	Any	PR[b]
↓100	Unequivocal progression	Any	PR[b]
↓≥ 50	Absent/Present/NA/ND [d]	Any	PR[b]
↓≥ 50	Unequivocal progression	Any	PR[b]
↓< 50 to < 25↑	Absent/Present/NA/ND [d]	Any	SD
↓< 50 to < 25↑	Unequivocal progression	Any	SD
≥ 25	Any	Any	PD[b]
UE	Any	Any	UE
ND	Any	Any	UE
NA[c]	Any	Any	UE

With:

Measurable Response	Non-measurable Response		Overall Response
Index and new, measurable lesions (tumor burden)[a], %	Non-index	New, non-measurable lesions	Using irRC
↓100	Absent/NA[d]	Absent	CR[b]
↓100	Present/ND**/UE**	Any	PR[b]
↓100	Unequivocal progression	Any	PR[b]
↓≥ 50	Absent/Present/NA[d]/ND**/UE**	Any	PR[b]
↓≥ 50	Unequivocal progression	Any	PR[b]
↓< 50 to < 25↑	Absent/Present/NA[d]/ND**/UE**	Any	SD
↓< 50 to < 25↑	Unequivocal progression	Any	SD
≥ 25	Any	Any	PD[b]
UE	Any	Any	UE
ND	Any	Any	UE
NA[c]	Any	Any	UE

Section: 14, Appendix D, Modified Immune-related Response Criteria (irRC) for Review of Disease Response in Phase 1b, Response Confirmation, Paragraph 5

Replace:

A best overall response of SD requires a visit response of SD or better no earlier than 77 days after the date of enrollment; otherwise the overall response will be UE.

With:

A best overall response of SD requires a visit response of SD or better no earlier than **84** days after the date of enrollment; otherwise the overall response will be UE.

Section: 14, Appendix F, Modified irRC-RECIST Guidelines for Assessment of Disease Response in Phase 3, Evaluation of Objective Response:, Table 16

Replace:

Measurable Response	Non-measurable Response		Overall Response
Target and new, measurable lesions (tumor burden)[a], %	Non-target	New, non-measurable lesions	Using modified irRC-RECIST
↓100[e]	Absent/NA[d]	Absent	iCR[b]
↓100	Present/ND	Any	iPR[b]
↓100	Unequivocal progression	Any	iPR[b]
↓≥ 30	Absent/Present/NA/ND [d]	Any	iPR[b]
↓≥ 30	Unequivocal progression	Any	iPR[b]
↓< 30 to ↑< 20	Absent/Present/NA/ND [d]	Any	iSD
↓< 30 to ↑< 20	Unequivocal progression	Any	iSD
↑≥ 20[f]	Any	Any	iPD[b]
iUE	Any	Any	iUE
ND	Any	Any	iUE
NA[c]	Any	Any	iUE

With:

Measurable Response	Non-measurable Response		Overall Response
Target and new, measurable lesions (tumor burden)[a], %	Non-target	New, non-measurable lesions	Using modified irRC-RECIST
↓100[e]	Absent/NA[d]	Absent	iCR[b]
↓100	Present/ND/**iUE**	Any	iPR[b]
↓100	Unequivocal progression	Any	iPR[b]
↓≥ 30	Absent/Present/NA[d]/ND/**iUE**	Any	iPR[b]
↓≥ 30	Unequivocal progression	Any	iPR[b]
↓< 30 to ↑< 20	Absent/Present/NA[d]/ND/**iUE**	Any	iSD
↓< 30 to ↑< 20	Unequivocal progression	Any	iSD
↑≥ 20[f]	Any	Any	iPD[b]
iUE	Any	Any	iUE
ND	Any	Any	iUE
NA[c]	Any	Any	iUE

Section: Appendix F, Modified irRC-RECIST Guidelines for Assessment of Disease Response in Phase 3, Evaluation of Objective Response:, Paragraph 4

Replace:

A best overall response of iSD requires a visit response of iSD or better no earlier than 77 days after the date of enrollment; otherwise the overall response will be unevaluable (iUE).

With:

A best overall response of iSD requires a visit response of iSD or better no earlier than **84** days after the date of enrollment; otherwise the overall response will be unevaluable (iUE).

Amendment 4

Protocol Title: A Phase 1b/3, Multicenter, Trial of Talimogene Laherparepvec in Combination With Pembrolizumab (MK-3475) for Treatment of Unresectable Stage IIIB to IVM1c Melanoma (MASTERKEY-265)

Amgen Protocol Number Talimogene Laherparepvec 20110265

EudraCT number 2014-000185-22

NCT Number 02263508

Amendment Date: 24 January 2018

Rationale:

The rationale for the major changes in this protocol are as follows:

- Replace the Dose Modification Guidelines for Pembrolizumab Related Adverse Events Table with the Pembrolizumab-related Adverse Event Management table to incorporate the new myocarditis risk and management;
- Replace the information and table regarding management of infusion reactions related to pembrolizumab to incorporate the most updated guidelines for grading, treatment and premedication at subsequent dosing;
- Remove redundant and outdated information about management of pembrolizumab-related adverse events from Section 6.2.2.3 to consolidate the dose modification and adverse event management into one table for easy reference;
- Add thyroid testing up to three days before dosing and explain that study treatment can be administered before the results are reported, as long as the subject is asymptomatic to facilitate study conduct at sites where thyroid testing results are not immediately available.

Other minor changes to the protocol for administrative and clarification purposes are as follows:

- Update the Key Sponsor Contact information
- Add clarity surrounding the response evaluation criteria used for Phase 1b and Phase 3 and the respective endpoints
- Clarify the collection of archival biopsy
- Clarify when subjects should undergo safety follow-up procedures
- Allow survival status to be assessed at additional time points not specifically outlined in the Schedule of Assessments

- Clarify that for subjects with progressive disease QLQ-C30 is not collected in the long-term follow-up; however, EQ-5D-3L will be collected through the long-term follow-up
- Clarify the timing of the beginning of the registry protocol
- Update the primary completion and end of trial dates
- Update talimogene laherparepvec background information based on recent published results
- Update pembrolizumab background information based on recent published results
- Update the rationale for combination therapy
- Clarify the timing of safety monitoring by the data monitoring committee
- Clarify that both clinical and photographic evaluations must be done for lesions which cannot be evaluated by radiographic imaging
- Clarify that prior tumor vaccines are allowable if administered in the adjuvant setting
- Allow subjects with latex allergies to use polyurethane condoms
- Clarify that the investigator should instruct the subject to return to the clinic within 3 days after notification of a suspected herpetic lesion
- Clarify that photographs of all visible lesions must be done at baseline to allow for follow-up of lesions during treatment
- Clarify that laboratory assessment up to 3 days prior to administration of study treatment is allowed
- Clarify which subjects will be included in the patient reported outcome analysis set
- Clarify how the futility analysis of overall survival for a non-constant treatment effect will be performed
- Update the references
- Update Appendix B to the most recent versions of the forms
- Update the matrix for determining the overall response at each assessment point for phase 1b and hase 3
- Make editorial, typographical, and formatting changes throughout the document

Amendment 3

Protocol Title: A Phase 1b/3, Multicenter, Trial of Talimogene Laherparepvec in Combination With Pembrolizumab (MK-3475) for Treatment of Unresectable Stage IIIB to IVM1c Melanoma (MASTERKEY-265)

Amgen Protocol Number (Talimogene Laherparepvec) 20110265

EudraCT Number: 2014-000185-22

NCT Number: 02263508

Amendment Date: 12 April 2017

Rationale:

This protocol is being amended to address changes in the statistical analyses for the following reasons:

- An event-driven overall survival interim analysis at 282 events (including a futility analysis) has now been added to the planned analyses in order to evaluate the efficacy/futility with approximately 70% power of the combination treatment at an earlier time point in order to facilitate regulatory submission if the combination demonstrates significant improvement in overall survival or stopping the study for futility in overall survival. The study team will conduct this analysis if it is unblinded after the progression free survival primary analysis, otherwise it will be conducted by the data monitoring committee.
- The interim futility analysis based on overall response rate and disease control rate for the data monitoring committee review was changed from the investigator assessment to a blinded independent central review. Using blinded independent central review assessed responses would provide a robust and consistent assessment of overall response rate and disease control rate as for the primary endpoint of progression free survival, which also utilizes blinded independent central review. The Bayesian priors for the combination arm were also revised to reflect new data available from the phase 1b part of the study.

To this end, the primary changes within this protocol are the following:

- Add an event-driven overall survival interim analysis at 282 events (including futility analysis).
- Revise overall response rate/disease control rate futility analysis.
- Replace the fallback procedure to test overall survival and progression free survival dual primaries with the Maurer-Bretz multiple testing procedure.
- Update secondary objectives to test additional hypotheses per modified irRC-RECIST by blinded independent central review, and overall survival excluding stage IVM1c.
- Update secondary and exploratory objectives related to patient reported outcomes.

In addition, minor clarifications, typographical and formatting changes were made throughout the protocol. Updates have been implemented to align with the current template.

Amendment 2

Protocol Title: A Phase 1b/3, Multicenter, Trial of Talimogene Laherparepvec in Combination With Pembrolizumab (MK-3475) for Treatment of Unresectable Stage IIIB to IVM1c Melanoma (MASTERKEY-265)

Talimogene Laherparepvec

Amgen Protocol Number (Talimogene Laherparepvec) 20110265

Amendment 2 Date: 25 September 2015

Rationale:

The protocol is amended primarily so that an injectable placebo may be added to pembrolizumab in the control arm and to convert the study from open-label to double-blind in phase 3. This is necessary in order to reduce the bias of having intralesional injections in only 1 arm of the study.

The following key changes have been incorporated into protocol amendment 2:

- Changed phase 3 portion of study to be double-blind and added placebo to the pembrolizumab arm. The placebo and talimogene laherparepvec will not be initially available as blinded investigational medicinal product. Until talimogene laherparepvec or placebo is available as blinded investigational medicinal product, the site pharmacist or designee will need to be unblinded to prepare blinded talimogene laherparepvec/placebo. The subject, Amgen study personnel, and all other site personnel and designees will be blinded to the randomization treatment group.
- Reordered sections to separate phase 1b and phase 3 in the synopsis, inclusion criteria, and general study procedures sections in order to more clearly delineate which sections are specific to each phase of the study.
- Updated background information for talimogene laherparepvec and pembrolizumab to reflect recent publications or presentations.
- Added results of the completed dose level review team (DLRT) evaluation for phase 1b.
- Allowed for more flexibility in frequency of radiographic follow-up for subjects who have reached a confirmed clinical response (CR) in long term follow-up. Subjects who have reached a confirmed CR may need less radiographic imaging per investigator discretion after prolonged periods of CR.
- Updated contraception language for exclusion criterion and also sections related to pembrolizumab. This is to align with other pembrolizumab protocols.
- Shortened period from ending prior adjuvant therapy from 3 months to 28 days prior to enrollment as 28 days should be adequate time for washout of the previous therapy.

- Prior ipilimumab as adjuvant therapy is now allowed. There may have been subjects that had disease recurrence following adjuvant ipilimumab for melanoma, and these subjects should not necessarily be excluded because ipilimumab has been received prior to pembrolizumab by many subjects in other studies and in clinical practice.
- Added exclusion criteria for allogeneic hematopoietic stem cell transplantation and for active tuberculosis in order to align with other pembrolizumab protocols.
- Updated text related to pembrolizumab events of clinical interest, rescue medications, dose adjustment, overdose, and supportive care guidelines to align with other pembrolizumab protocols. Immune-related adverse events are no longer considered pembrolizumab events of interest, but diffuse liver injury and pembrolizumab overdose are still events of clinical interest.
- Combined the tables for the schedule of assessments for phase 3; arms 1 and 2, since the study procedures will be identical for both arms of the study.
- Injectable investigational product-related adverse events during the long-term follow-up period will be collected. Although there is a talimogene laherparepvec registry protocol capturing reporting of any long-term talimogene laherparepvec-related adverse events, the subjects would not be eligible to enroll in this registry protocol until after they have ended their participation on this study. Subjects may be in long-term follow-up for many years prior to participation in the registry, and this change will allow for reporting of long-term talimogene laherparepvec-related adverse events during the long-term follow up period between the safety follow-up period and the time that the subjects can enroll on the registry protocol.
- Updated pregnancy and lactation reporting language to align with other talimogene laherparepvec and pembrolizumab protocols.
- Updated text for interim analysis and interim objective response rate (ORR) futility analysis in phase 3. In the event that futility is declared on ORR at the interim futility analysis, disease control rate (DCR) would also need to have futility declared. This is to prevent the study treatment being declared futile when the ORR may not be adequately improved but the DCR is at the time of the interim analysis.
- Updated text pertaining to the analysis for the secondary endpoint of progression-free survival (PFS) per immune-related response criteria simulating Response Evaluation Criteria in Solid Tumors (irRC-RECIST) (phase 3) and including text regarding multiplicity adjustment for further clarification.
- Removed from modified RECIST 1.1 criteria used for blinded independent central review the modification that new skin lesions will be considered in the overall non-target lesion assessment but will not automatically result in a timepoint response of progressive disease (PD) in order to more closely follow conventional RECIST 1.1.
- Updated language to clarify the modified response criteria in the appendices (eg, the maximum number of new measurable lesions that may be added, how to evaluate resected lesions).

Amendment 1

Protocol Title: A Phase 1b/3, Multicenter, Open-label Trial of Talimogene Laherparepvec in Combination With Pembrolizumab (MK-3475) for Treatment of Unresected, Stage IIIB to IVM1c Melanoma (MASTERKEY)

Talimogene Laherparepvec

Amgen Protocol Number 20110265

Amendment Date: 15 May 2015

Rationale:

The protocol has been amended to adequately power the study to evaluate the efficacy of talimogene laherparepvec in combination with pembrolizumab in subjects with unresected, stage IIIB to IVM1c melanoma to support approval of talimogene laherparepvec in combination with pembrolizumab in this patient population.

The following are the key changes incorporated into protocol amendment 1:

- Changed the phase 2 part of study to phase 3
- Included 2 primary endpoints, progression-free survival (PFS) and overall survival (OS), in phase 3. The primary end of PFS will be based on tumor evaluation by an independent blinded central review using modified RECIST 1.1.
- RECIST 1.1 including the following modifications will be used by a blinded independent central review for determination of primary endpoint and some of the secondary tumor response-related endpoints in the phase 3 part of the study:
    1. increased total target lesions to a maximum of 10 (up to a maximum of 5 per organ).
    2. because appearance of new skin lesions may not necessarily correlate with clinically relevant disease progression, new skin lesions will be considered in the overall non-target lesion assessment, but will not automatically result in a timepoint response of progressive disease
- Removed cross-over combination treatment (Phase 2 Part 2) for subjects who progress on the pembrolizumab control arm in the randomized portion in order to better study the primary endpoint of OS.
- Increased sample size of phase 3 from 90 to 660 subjects to formally test for PFS and OS as 2 primary endpoints

- Revised the treatment schedule of pembrolizumab during the phase 3 to 200 mg every 3 weeks in phase 3. This was due to data from comparisons of every 2 week to every 3 week dosing of pembrolizumab which showed comparable efficacy, safety, and pharmacokinetics between the two groups.
- Revised the phase 3 treatment schedule of talimogene laherparepvec to up to 4 mL 10^6 PFU/mL at week 0, followed by up to 4 mL of 10^8 PFU/mL at weeks 3, 5, 7, 9, and then every 3 weeks. The every 2 week schedule weeks 3-9 is preserved in order to allow for more optimal delivery of talimogene laherparepvec during the period when most subjects will have lesions to inject, but increased to every 3 weeks after week 9 in order to synchronize the schedules of talimogene laherparepvec for longer term dosing.
- Updated the prior therapy inclusion criteria in phase 3 as described below to account for the increasing use of BRAF inhibitor regimens in the first line for $BRAF^{V600}$ mutant melanoma :
  - Subjects with $BRAF^{V600}$ wild-type tumors must not have received any prior systemic anticancer treatment consisting of chemotherapy, immunotherapy, or targeted therapy for unresected stage IIIB to IVM1c melanoma.
  - Subjects with $BRAF^{V600}$ mutated tumors who have received prior BRAF inhibitor therapy either alone or in combination with MEK inhibitor as their only prior systemic therapy are eligible for this study. However, the subject must have ended BRAF inhibitor therapy either alone or in combination with MEK inhibitor at least 14 days prior to enrollment. At the discretion of the investigator, subjects with $BRAF^{V600}$ mutant melanoma or those subjects whose $BRAF^{V600}$ mutation status is unknown at the time of randomization who have not received a BRAF inhibitor are also eligible for the phase 3 of this study as first-line treatment if they meet the following criteria: LDH < ULN, no clinically significant tumor related symptoms in the judgment of the investigator, and absence of rapidly progressing metastatic melanoma in the judgment of the investigator.
  - Subjects who received prior adjuvant therapy for melanoma will not be excluded (including, but not limited to, interferon, limb infusion/perfusion, or use of investigational agents in the adjuvant setting). However, the subject must have ended therapy at least 3 months prior to enrollment.
  - No prior pembrolizumab, other anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, ipilimumab, other CTLA-4 inhibitor, talimogene laherparepvec, tumor vaccine, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways is allowed, even if given in the adjuvant setting.
- For treatment decisions and secondary endpoints, sed immune-related response criteria simulating-RECIST (irRC-RECIST) in phase 3 which reduces tumor measurements to a single dimension like conventional RECIST but can account for unique tumor response characteristics observed with immunotherapies to enable treatment beyond disease progression (PD), if the subject is clinically stable, until PD is confirmed at least 4 weeks after initial progression as a secondary endpoint.
- Given that subjects who have initial progression before response might still have clinical benefit from treatment and might be different between the two arms in phase 3, more formal testing of irRC-RECIST as a secondary endpoint is planned. An event-driven analysis of the secondary PFS endpoint based on irRC-RECIST per investigator will be tested at the earlier of the following outcomes: (1) a statistically significant improvement in the primary PFS endpoint with testing at a 2-sided 0.005

level, or (2) an interim or primary analysis statistically significant improvement in OS with testing at a 2-sided 0.045 level.

- Updated the measurable disease inclusion criteria in phase 3 as described below:
  - Measurable disease defined as either one of the following to better match RECIST criteria:
    - at least 1 visceral or nodal/soft tissue melanoma lesion that can be accurately and serially measured in at least 1 dimension and for which the longest diameter is ≥ 10 mm as measured by CT scan or MRI. Lymph nodes must measure ≥ 15 mm in their short axis to be considered measurable by CT scan or MRI

- Updated the inclusion criteria in phase 3 to require subjects to attempt collection of tumor samples (archival sample or newly obtained biopsy) that are adequate for PD-L1 assessment prior to randomization up to two times.

- Skin photographs and radiographs performed during the 3 part of the study will be collected and submitted to a blinded independent imaging vendor for evaluation of primary endpoint of PFS and secondary response-related endpoints by central review.

- Removed the option for retreatment (second-course phase) for subjects who initially stopped talimogene laherparepvec or pembrolizumab treatment after attaining investigator-confirmed complete response (CR) and later experienced an investigator-determined PD as evaluating retreatment after progression is not an objective of this study.

- The phase 1b will be re-analyzed after the last subject has had a chance to be followed for 24 weeks from the initiation of pembrolizumab and at the time of the phase 3 primary analysis in order to provide a interim review of efficacy data between the phase 1b and phase 3 primary analyses.

- Added 2 interim safety, 1 interim ORR futility, 1 interim efficacy, and 1 interim analysis for OS during the phase 3.

- Utilized an independent, external to Amgen and Merck, data monitoring committee (DMC) in phase 3 to monitor safety and evaluate futility.

- Updated the pembrolizumab-related pneumonitis toxicity management guidelines to incorporate instruction for management of interstitial lung disease (ILD) as described in the Dear Investigator Letter, dated 24 October 2014, and the Pembrolizumab Event of Clinical Interest and Immune-Related Adverse Events Guidance document version 3.0.
- Updated the tumor sample collection schedule during phase 3 as described below:
  - The following tumor samples will be to obtained from all subjects enrolled in phase 3:
    - A biopsy will be performed during screening
    - A formalin-fixed paraffin-embedded (FFPE) tumor tissue will collected during screening. No repeat tumor biopsy would be needed provided the (FFPE)

tumor tissue was obtained within 3 months of enrollment and there was no intervening therapy.

- At least a single post-treatment biopsy will be collected at week 5 from an uninjected lesion (preferred) or an injected lesion if there are no uninjected lesions available for biopsy.

– The following tumor tissue samples will be to obtained from approximately 200 subjects (100 per arm) enrolled in phase 3 at select sites:

- At least a single post-treatment biopsy will be collected at the time of confirmed disease progression.

- Revised the schedule of safety laboratory assessments (hematology, chemistry, thyroid function test, and urinalyses), patient-reported outcomes assessments (EQ-5D and EORTC QLQ-C30), pembrolizumab PK analyses, and anti-pembrolizumab antibody analyses to align with revised pembrolizumab treatment schedule during phase 3. The blood sample collection for pembrolizumab PK analyses and anti-pembrolizumab antibody analyses in phase 3 may be discontinued if ongoing PK and antibody results from this study continue to be consistent with existing PK and antibody data from other pembrolizumab melanoma clinical trials.
- The secondary objectives evaluating anti-pembrolizumab antibodies and pharmacokinetics of pembrolizumab as well as changes in PD-L1 expression in injected and non-injected lesions after starting talimogene laherparepvec have been converted into exploratory objectives so that there would be more emphasis on efficacy and safety objectives. The overall analysis for these objectives will not change.
- Ordinal categorical response score and deep response rate were removed as endpoints since they may be derived from objective response rate.
- Moved evaluation of patient reported outcomes (PRO) in the randomized phase from an exploratory to secondary objective for greater emphasis.
- Additional language is provided to clarify the responsibilities of the Dose Level Review Team (DLRT) in providing recommendations in phase 1b, but there are no changes in the DLRT responsibilities.
- Increased follow-up of subjects from 36 months to 60 months after the last subject is enrolled in order to ensure enough events would be captured for the overall survival endpoint.
- Changed the reporting period for pembrolizumab Events of Clinical Interest from 90 (+7) days after the last dose of pembrolizumab to 90 (+7) after the last of dose of pembrolizumab or 30 (+7) days after initiation of a new anticancer therapy, whichever is earlier, and changed the reporting period for serious adverse events from 90 (+7) days after the cessation of all study treatment to 90 (+7) days after the cessation of all study treatment or 30 (+7) days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, to align with other pembrolizumab protocols.

Other changes and administrative corrections were made throughout the protocol. Refer to the subsequent sections of this document for description of the changes incorporated in protocol amendment 1.