Title: A Phase 1b/2, Multicenter, Open-label, Basket Trial to Evaluate the Safety of Talimogene Laherparepvec Injected into Liver Tumors Alone and in Combination With Systemic Pembrolizumab in Phase 1b and to Evaluate the Efficacy and Safety of Intratumoral Talimogene Laherparepvec in Combination With Systemic Pembrolizumab to Treat Subjects With Advanced Solid Tumors in Phase 2 (MASTERKEY-318)

Amgen Protocol Number (Talimogene Laherparepvec 20140318)

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This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures. This format and content of this protocol is aligned with Good Clinical Practice: Consolidated Guidance (ICH E6).

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Investigator's Agreement

I have read the attached protocol entitled A Phase 1b/2, Multicenter, Open-label, Basket Trial to Evaluate the Safety of Talimogene Laherparepvec Injected into Liver Tumors Alone and in Combination With Systemic Pembrolizumab in Phase 1b and to Evaluate the Efficacy and Safety of Intratumoral Talimogene Laherparepvec in Combination with Systemic Pembrolizumab to Treat Subjects with Advanced Solid Tumors in Phase 2 (MASTERKEY-318), dated **26 October 2021**, 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/2, Multicenter, Open-label, Basket Trial to Evaluate the Safety of Talimogene Laherparepvec Injected into Liver Tumors Alone and in Combination with Systemic Pembrolizumab in Phase 1b and to Evaluate the Efficacy and Safety of Intratumoral Talimogene Laherparepvec in Combination with Systemic Pembrolizumab to Treat Subjects with Advanced Solid Tumors in Phase 2 (MASTERKEY-318)

Study Phase: 1b/2

Indication:
Part 1 (NOTE: as of Protocol Amendment 6 [dated 26 October 2021], intrahepatic injections of talimogene laherparepvec and liver biopsies are no longer performed in this study):

Intrahepatic injection of talimogene laherparepvec into metastatic liver tumors (non-HCC) and hepatocellular carcinoma (HCC)

Part 2:

Intratumoral injection of talimogene laherparepvec into cutaneous, subcutaneous, lymph node, or liver tumors

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Primary Objectives:

Part 1 (NOTE: as of Protocol Amendment 6 [dated 26 October 2021], intrahepatic injections of talimogene laherparepvec and liver biopsies are no longer performed in this study):

To evaluate the following, as assessed by the incidence of dose-limiting toxicities (DLTs), in subjects with liver metastases (non-hepatocellular carcinoma [HCC]) and subjects with primary HCC in:

- Monotherapy Cohorts: the maximum tolerated volume and concentration (MTV and MTC) of intrahepatic injection of talimogene laherparepvec into liver tumors in subjects with non-HCC and subjects with primary HCC without active viral hepatitis
- Combination Cohorts: the MTC of intrahepatic injection of talimogene laherparepvec into liver tumors in combination with systemic intravenous (IV) administration of pembrolizumab in subjects with non-HCC, and subjects with primary HCC with or without viral hepatitis

Part 2:

- To evaluate the efficacy, as assessed by objective response rate (ORR) of intratumoral injection of talimogene laherparepvec in combination with systemic IV administration of pembrolizumab, separately, for each non-HCC tumor type (hormone receptor positive breast adenocarcinoma [BC], triple negative breast cancer [TNBC], colorectal adenocarcinoma [CRC], cutaneous squamous cell carcinoma (CSCC)], basal cell carcinoma [BCC], as well as primary HCC with and without viral hepatitis.
- To evaluate safety separately for each tumor type as assessed by subject incidence of treatment-emergent and treatment-related adverse events, including DLTs

Secondary Objectives: The secondary objectives of the study are as follows:

EFFICACY:

Part 1:

To evaluate the efficacy separately by monotherapy versus combination for non-HCC tumors and HCC with and without viral hepatitis when applicable as assessed by:

- ORR, best overall response (BOR), durable response rate (DRR), duration of response (DOR), response in injected and uninjected lesions, disease control rate (DCR), progression-free survival (PFS), and overall survival (OS)

Part 2:

- To evaluate the efficacy in individual tumor types in the non-HCC group and HCC group with and without viral hepatitis as assessed by:
  - BOR, DRR, DOR, response in injected and uninjected lesions, DCR, PFS, and OS by primary tumor type (TNBC, Hormone receptor positive BC, CRC, CSCC, BCC, and HCC with and without viral hepatitis)

SAFETY (Parts 1 and 2)

- To evaluate the safety in each monotherapy and combination cohorts in Part 1 and each arm separately in Part 2, as assessed by subject incidence of treatment-emergent and treatment-related adverse events
- To estimate the incidence of detectable talimogene laherparepvec deoxyribonucleic acid (DNA) in blood and urine
- To estimate the incidence of clearance of talimogene laherparepvec DNA from blood and urine
- To estimate the rate of detection (per sample) and incidence (per subject) of talimogene laherparepvec DNA and virus at the surface of talimogene laherparepvec injection site, the exterior of occlusive dressing, and the oral mucosa
- To estimate the incidence of talimogene laherparepvec DNA detection in lesions suspected to be herpetic in origin

Clinical Hypotheses:

Part 1:

Monotherapy cohorts 1-4: Talimogene laherparepvec injected intrahepatically into liver tumors will be safe in subjects with non-HCC with liver metastases and subjects with HCC without active viral hepatitis as assessed by subject incidence of DLTs.

Combination cohorts 5 and 6: Talimogene laherparepvec injected intrahepatically into liver tumors in combination with systemically administered pembrolizumab will be safe in subjects with non-HCC with liver metastases and subjects with HCC with and without viral hepatitis.

Part 2:

Talimogene laherparepvec injected intratumorally in combination with systemic IV administration of pembrolizumab will demonstrate at least a 40% ORR in each tumor type and be safe in the non-HCC tumor types as well as primary HCC with and without viral hepatitis.

Primary Endpoint:

Part 1:

Monotherapy cohorts 1-4: Subject incidence of DLTs with intrahepatic injection of talimogene laherparepvec into liver tumors in subjects with non-HCC with liver metastases and subjects with HCC without active viral hepatitis.

Combination cohorts 5 and 6: Subject incidence of DLTs with intrahepatic injection into liver tumors of talimogene laherparepvec in combination with systemic IV administration of pembrolizumab in subjects with non-HCC with liver metastases and subjects with HCC with and without viral hepatitis as assessed by subject incidence of DLTs.

Part 2:

- ORR per the modified immune-related response criteria simulating Response Evaluation Criteria in Solid Tumors version 1.1 (irRC-RECIST) with intralesional injection of talimogene laherparepvec into cutaneous, subcutaneous, lymph node, and liver tumors in combination with systemic IV administration of pembrolizumab separately by tumor type arm (TNBC, Hormone receptor positive BC, CRC, CSCC, BCC, and HCC with and without viral hepatitis)

- Subject incidence for each tumor type of treatment-emergent and treatment-related adverse events, including DLTs

Secondary Endpoints:

Efficacy:

Part 1:

- ORR, BOR, DRR, DOR, response in injected and uninjected lesions, DCR, PFS, and OS separately for non-HCC and HCC tumors in monotherapy and combination cohorts

Part 2:

- BOR, DRR, DOR, response in injected and uninjected lesions, DCR, PFS, and OS by primary tumor type arm (TNBC, Hormone receptor positive BC, CRC, CSCC, BCC, and HCC with and without viral hepatitis)

Safety:

Parts 1 and 2:

- Subject incidence of treatment-related and treatment-emergent adverse events (monotherapy and combination cohorts in Part 1, and each tumor type separately in Part 2, and HCC with and without viral hepatitis)
- Subject incidence of detectable talimogene laherparepvec DNA in blood and urine
- Incidence of clearance of talimogene laherparepvec DNA from blood and urine
- Subject incidence (per subject) and rate of detection (per sample) of talimogene laherparepvec DNA and virus at the surface of injection site, the exterior of occlusive dressing, and the oral mucosa
- Subject incidence of talimogene laherparepvec DNA detection in lesions suspected to be herpetic in origin

Study Design: This is a phase 1b/2, multicenter, open-label, basket trial to evaluate the safety of talimogene laherparepvec injected intrahepatically into liver tumors alone and in combination with systemic IV administration of pembrolizumab, in subjects with non-HCC liver metastases from BC, CRC, gastroesophageal cancer (GEC), melanoma, NSCLC, RCC in Part 1 Group A, and subjects with HCC with and without viral hepatitis in Part 1 Group B (viral hepatitis is only applicable in combination setting), and to evaluate the efficacy and safety of intratumoral talimogene laherparepvec in combination with systemic pembrolizumab in subjects with advanced TNBC, hormone receptor positive breast cancer, CRC, CSCC, and BCC in Part 2 Group A and subjects with HCC with and without viral hepatitis in Part 2 Group B. The study consists of 2 parts and 2 groups, and Part 2 includes 2 stages.

The objective of Part 1 is to evaluate the safety of intrahepatic injection of talimogene laherparepvec into liver tumors alone and in combination with systemically administered pembrolizumab for the non-HCC (Group A) and HCC (Group B [with and without viral hepatitis; viral hepatitis is only applicable in combination setting]) cohorts separately. **NOTE: as of Protocol Amendment 6 [dated 26 October 2021], intrahepatic injections of talimogene laherparepvec and liver biopsies are no longer performed in this study.** In the monotherapy cohorts (Cohorts 1-4), the safety of administering increasing concentration (10^7 plaque forming unit [PFU]/mL or 10^8 PFU/mL) and volumes (maximum up to 4 or 8 mL) of talimogene laherparepvec will be determined using a standard 3 + 3 design. The concentration of the first dose of talimogene laherparepvec in all cohorts is always 10^6 PFU/mL. Cohort 1 of Group B will be initiated only after safety has been established in Cohort 1 of Group A.

Combination cohorts (Cohorts 5 and 6) in Part 1 will determine the safety of administering intrahepatic injection of talimogene laherparepvec at 10^7 PFU/mL or 10^8 PFU/mL in sequential cohorts (volume up to 4 mL for both doses) in combination with systemic IV administration of

pembrolizumab (200 mg). A modified toxicity probability interval (mTPI) up-and-down design will be used to determine safety in the combination cohorts.

Once the MTC is determined from Cohorts 5 and 6, Part 2 will open to evaluate efficacy and safety of the combination treatment in the respective tumor types (5 non-HCC tumor types in Group A and HCC tumor type in two cohorts [with and without viral hepatitis] in Group B). Timing of opening Part 2 for the non-HCC (Group A) and HCC (Group B) groups will be based on when the MTC for talimogene laherparepvec (from the combination cohorts) is determined for the respective Groups. Talimogene laherparepvec will be used at a maximum volume of 8 mL (established from monotherapy Cohort 3 in Part 1). If the safety of administering up to 8 mL from the monotherapy cohorts is not established at the time of opening Part 2, newly enrolled subjects in Part 2 will be allowed to receive up to a maximum of 8 mL, only if and when, safety of administering 8 mL in monotherapy from Part 1 is established. No intrasubject concentration or volume escalation is allowed.

Cohorts in Part 1	Talimogene laherparepvec Volume (mL)	Initial Talimogene Laherparepvec Concentration (PFU/mL)	Second and Subsequent Talimogene Laherparepvec Concentration (PFU/mL)	Pembrolizumab dose (mg)
1	4	10^6	10^7	n/a
2[a]	4	10^6	10^8	n/a
3[b]	8	10^6	10^8	n/a
4[c]	8	10^6	10^7	n/a
5	4	10^6	10^7	200
6[d]	4	10^6	10^8	200

DLT = dose-limiting toxicity; n/a = not applicable; PFU = plaque forming unit
[a] If Cohort 6 is deemed safe, then cohort 2 will stop enrolling in the respective Group
[b] If Cohort is deemed safe in either Group A or B, further enrollment into cohort 3 into either group will be suspended, then up to 8 ml will be used in Part 2 for Group A and B.
[c] Cohort will be opened only if one of these conditions are met: 1) DLT rate ≥ 1/3 in Cohort 2; 2) DLT rate ≥ 1/3 in Cohort 3 and Part 2 dose for talimogene laherpare**p**vec not determined yet; or 3) DLT rate ≥ 1/3 in Cohort 3 and Part 2 concentration for talimogene laherparepvec is determined to be 10^7 PFU/mL
[d] Includes Group B Cohort 6a and Cohort 6b

Part 2 consists of 2-stage design to evaluate the efficacy and safety of talimogene laherparepvec in combination with systemic pembrolizumab. Efficacy and safety will be evaluated in each of the 5 non-HCC tumor types from Group A separately. Similarly, the efficacy and safety of the combination treatment will be determined for Group B HCC subjects with and without viral hepatitis. The primary analysis of efficacy will include subjects that receive any volume of talimogene laherparepvec and pembrolizumab. In Stage 1 of Part 2, enrollment into a tumor type (arm) will stop for efficacy analysis when 10 subjects with that tumor type are enrolled. If efficacy for that tumor type is not futile, Stage 2 can open where an additional 11 subjects can be enrolled for that tumor type arm. The Dose Level Review Team (DLRT) will consider prospective guidelines to monitor safety in Part 2 separately by tumor type and, if introduced, talimogene laherparepvec total volumes > 4 mL within Group A and Group B.

For details on study design, please refer to the Study Design and Treatment Schema and Section 3.1.

Sample Size: Total number of subjects **enrolled** in Part 1 and Part 2 of the study is **127** subjects (**74** subjects in Part 1; **53** subjects in Part 2). The Part 2 efficacy will include all treated subjects who received at least one dose of talimogene laherparepvec and pembrolizumab; therefore, dose-limiting toxicity non-evaluable subjects will not be replaced in Part 2.

Summary of Subject Eligibility Criteria:

Key Inclusion Criteria:

Subjects must be age ≥ 18 years at the time of informed consent. Subjects must have histologically or cytologically confirmed disease.

- Part 1 is restricted to BC, CRC, GEC, melanoma, NSCLC, or RCC with liver metastases or HCC.
- Part 2 Group A is restricted to advanced hormone receptor positive BC, CRC, TNBC, CSCC, and BCC with or without liver metastases.
  - Part 2 Hormone receptor positive Breast Cancer Arm only: Histologically and/or cytologically confirmed diagnosis of estrogen receptor (ER) positive and/or progesterone receptor (PrR) positive (ER ≥ 1%, PrR ≥ 1%) breast cancer.
  - Triple negative breast cancer: Histologically and/or cytologically confirmed diagnosis of ER negative, PR negative, human epidermal growth factor receptor 2 (HER2)-Neu negative (ER <1%; PR <1%; HER2-Neu < 3+ by immunohistochemistry or fluorescence in situ hybridization ratio ≤ 2.2 or < 6 copies HER2 gene copies/nucleus).
- Part 2 Group B is restricted to HCC (fibrolamellar and mixed hepatocellular/cholangiocarcinoma subtypes are not eligible).

For HCC subjects with a diagnosis of hepatitis B, they must be on hepatitis antiviral therapy for at least 4 weeks prior to enrollment and HBV viral load by real-time polymerase chain reaction (qPCR) must be ≤ 100 IU/mL. HCC subjects with past or ongoing hepatitis C infection must have completed treatment for hepatitis C at least 1 month prior to study enrollment and hepatitis C viral load must be undetectable; subjects with hepatitis B and C must fulfill the eligibility criteria for hepatitis B and hepatitis C. Subjects with locally recurrent TNBC are eligible.

Non-HCC subjects must have received at least 1 prior standard of care systemic anti-cancer therapy for their locally advanced or metastatic disease. For the combination cohorts (Cohorts 5 and 6 in Part 1) and Part 2, subjects with melanoma CSCC or NSCLC do not need to have received prior therapy. In Part 1, subjects must have measurable liver tumors and liver tumors that are suitable for injection. In Part 2, subjects must have measurable disease and cutaneous, subcutaneous, lymph node, or liver tumors suitable for injection. Eastern Cooperative Oncology Group (ECOG) performance status must be 0 or 1, and life expectancy should be approximately 5 months or more. Adequate hematological, renal, hepatic, and coagulation function is required. Liver function tests may be mildly abnormal but within the parameters defined in Section 4.1.1. Child-Pugh score must be A.

Key Exclusion Criteria:

Subjects must not be candidates for surgery or locoregional therapy with curative intent or planned systemic anti-cancer therapy, with the exception of immunotherapy in the combination cohorts (Cohorts 5 and 6 in Part 1 and all subjects in Part 2). Liver tumors must not be estimated to invade approximately more than one-third of the liver. Liver tumor-directed therapy, hepatic surgery or major surgery, antibody-based therapy, or immunotherapy must not have been performed < 28 days, chemotherapy < 21 days, and targeted small molecule therapy or hormonal therapy < 14 days prior to enrollment. Subjects must either (1) have no central nervous system (CNS) metastasis, or carcinomatous meningitis, or (2) if CNS metastasis is present, must have stable treated cerebral metastases from BC, NSCLC, RCC, CRC, GEC, or melanoma. Subjects must not have symptomatic auto-immune disease or be symptomatically immunosuppressed. They must not have a history of solid organ transplantation. For non-HCC, there must not be acute or chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. For HCC with prior hepatitis B and/or C infection, HBV and/or HCV viral load by qPCR must be undetectable, and they must not have had recent treatment within 12 weeks for HBV or HCV with certain antiviral medications in Part 1 Group B cohorts 1-5 and 6a, and Part 2 Group B HCC without viral hepatitis. For all patients in Part 1 and for patients in Part 2 where intrahepatic liver injection is planned **(NOTE: as of Protocol Amendment 6 [dated 26 October 2021], intrahepatic injections of talimogene laherparepvec and liver biopsies are no longer**

performed in this study), there should be no macroscopic intravascular invasion of tumors into the main portal vein, hepatic vein, or vena cava. Subjects must not: have active herpetic skin lesions or prior complications of herpetic infection (eg, herpetic keratitis or encephalitis); require treatment with an antiherpetic drug; have received live-virus vaccination within 30 days of planned treatment start; have previous therapy with talimogene laherparepvec, oncolytic viruses, or tumor vaccine. They must not require concomitant treatment with warfarin. Subjects in the combination treatment cohort must not have: a history or evidence of psychiatric, substance abuse, or any other clinically significant disorder; toxic effects of the most recent prior chemotherapy not resolved to grade 1 or less (except alopecia); or expected other cancer therapy while on study with the exception of local radiation to the site of bone or other metastasis for palliative treatment. Male subjects of reproductive potential in the combination treatment must be willing to use acceptable methods of effective contraception during treatment and through 4 months after the last dose of pembrolizumab.

For a full list of eligibility criteria, please refer to Section 4.1.

Investigational Product

In Part 1, talimogene laherparepvec will be administered by image guided injection (either by ultrasound [US] or computed tomography [CT] scan) into injectable liver lesions only. In Part 2, talimogene laherparepvec can be administered into liver lesions, lymph nodes, cutaneous or subcutaneous lesions (non-hepatic lesions). **As of Protocol Amendment 6 (dated 26 October 2021), intrahepatic injections of talimogene laherparepvec and liver biopsies are no longer performed in this study.** It is mandatory that administration into liver lesions or is by image guided injection (either by US or CT scan). Image guidance may also be used for other non-hepatic intratumoral injections. Dosing concentrations and volumes will be determined during dose escalation in Part 1. The initial concentration for all subjects will be at 10^6 PFU/mL. Twenty-one (+ 3) days later, either 10^7 or 10^8 PFU/mL will be given. Subsequent doses will be given every 21 days (Q21D; ± 3 days) thereafter. The volume will be either up to 4 mL or 8 mL. For Part 1, up to 6 doses of talimogene laherparepvec may be administered (including 10^6 PFU/mL dose), and there is an investigator option to continue for up to 6 additional doses Q21D (± 3 days). Additional cycles of talimogene laherparepvec may be given in combination with pembrolizumab in Part 2 if the investigator determines the subject is having clinical benefit and approval from the sponsor medical monitor is obtained. In Part 2, a maximum of 35 cycles of talimogene laherparepvec will be administered Q21D (± 3 days). Talimogene laherparepvec will be provided at either 10^6 PFU/mL or 10^8 PFU/mL concentrations. The 10^7 PFU/mL concentration will be prepared from the 10^8 PFU/mL concentration diluted 1:10.

See Section 6.2.1 for additional information regarding dosage and administration of talimogene laherparepvec.

Pembrolizumab at a dose of 200 mg will be administered every 3 weeks (Q3W; ± 3 days) using 30-minute IV infusion. When talimogene laherparepvec and pembrolizumab are administered on the same day, talimogene laherparepvec should be administered first, if possible.

Subjects can receive up to 35 cycles (approximately 24 months) with pembrolizumab. During that time, subjects may continue until progressive disease (PD) per the modified irRC-RECIST (Appendix D), unacceptable toxicity, withdrawal of consent, physician's decision to stop therapy for the subject, or sponsor's decision to terminate the study. Discontinuation of treatment may be considered for subjects who have attained a confirmed complete response (CR) that have been treated for at least 8 cycles (24 weeks) with pembrolizumab, and had at least 2 cycles of pembrolizumab beyond the date when the initial CR was declared.

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

Procedures:

Screening Procedures:

The following procedures are to be completed during the screening period at the time points indicated in the Schedule of Assessments (Table 8 and Table 10)

- Confirmation that the informed consent form (ICF) has been signed and registration of screening in Interactive Voice Response (IVR) system followed by review of eligibility, medical and surgical history, demographic data, vital signs, physical examination per standard of care including body weight, ECOG performance status, electrocardiogram (ECG), and Child-Pugh score
- Laboratory assessments: hematology panel; chemistry panel; coagulation tests; lactate dehydrogenase (LDH); hepatitis serology including HBV, and HCV panel; qualitative serum or urine pregnancy testing for women of childbearing potential;carcinoembryonic antigen (CEA) in CRC and GEC adenocarcinoma only; alpha fetoprotein (AFP) in HCC only; cancer antigen 19-9 (CA 19-9) (Part 1 only) in CRC, GEC, and HCC only; and thyroid function tests (combination treatment only)
- Disease specific assessments (see Section 7.2.1)
- For subjects in Part 1, liver tumor biopsy unless already performed as standard of care. For subjects in Part 2, tumor biopsy unless already performed as standard of care.
- Radiographic and clinical (if applicable) tumor assessment
- Documentation of concomitant medications
- Review of serious adverse events

Treatment Procedures:

The following procedures will be completed during the treatment at the times designated in the Schedule of Assessments (Table 8 through Table 13)

- Vital signs, physical examination including weight, and ECOG performance status
- Local laboratory assessments: hematology panel, chemistry panel, LDH, coagulation tests, CEA in CRC and GEC adenocarcinoma only, AFP in HCC only, CA 19-9 (Part 1 only) in CRC, GEC, and HCC only, HBV DNA by qPCR or HCV RNA by PCR for subjects with history of or chronic HBV or HCV infection, respectively
- Combination treatment only (Part 1 Cohorts 5 & 6 and Part 2): Thyroid Function Tests (triiodothyronine [T3] or free triiodothyronine [FT3], free thyroxine [FT4] and thyroid-stimulating hormone [TSH])

  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
- Central laboratory assessments: [redacted], herpes simplex virus type 1 (HSV-1) immunoglobulin G (IgG) antibody serostatus, and blood and urine for qPCR testing for talimogene laherparepvec DNA; swabs of the injection site, exterior of occlusive dressing, and oral mucosa for qPCR testing of talimogene laherparepvec DNA with or without 50% Tissue Culture Infective Dose ($TCID_{50}$) assay for talimogene laherparepvec virus; swabs of cold sores, vesicles and other lesions suspected to be herpetic in origin (if any) for qPCR testing of talimogene laherparepvec DNA.
- In Part 1, biopsies of injected and, when available, uninjected liver tumors for [redacted] In Part 2, biopsies of injected and, when available, uninjected tumors for [redacted]. **As of Protocol Amendment 6 (dated 26 October 2021), liver biopsies are no longer performed in this study**.
- Radiographic tumor assessments, clinical tumor assessment and tumor response assessments by modified irRC-RECIST (Appendix D)
- Reporting disease related events, adverse events, serious adverse events, and documentation of concomitant medications
- Administration of study treatment (refer to Section 6) with observation period, where applicable. **As of Protocol Amendment 6 (dated 26 October 2021), intrahepatic injections of talimogene laherparepvec are no longer performed in this study.**

- Reporting potential or known unintended exposure to talimogene laherparepvec as specified in Section 9.4

Safety Follow-up Procedures:

Upon permanent discontinuation from the study treatment for any reason, the following procedures will be performed 30 (+7) days after the last dose of talimogene laherparepvec for the monotherapy cohorts (Cohorts 1, 2, 3 and 4, in Part 1); and will be performed 30 (+ 7) days after the last dose of talimogene laherparepvec or pembrolizumab, whichever is later, for the combination treatment (Cohorts 5 and 6 in Part 1 and all arms in Part 2):

- Vital signs, physical examination including weight, ECOG, and ECG
- Local laboratory assessments: hematology panel, chemistry panel, LDH, coagulation tests, serum or urine pregnancy test for females of childbearing potential, CEA in CRC and GEC adenocarcinoma only, AFP in HCC only, CA 19-9 (Part 1 only) in CRC, GEC, HCC only, HBV DNA by PCR or HCV RNA by PCR for subjects with history of or chronic HBV or HCV infection, respectively
- Child-Pugh score
- Central laboratory assessments: [redacted], HSV-1 IgG antibody serostatus, and qPCR testing for talimogene laherparepvec DNA; urine for qPCR testing of talimogene laherparepvec DNA; swabs of the oral mucosa for qPCR testing of talimogene laherparepvec DNA; swabs of cold sores, vesicles and other lesions suspected to be herpetic in origin (if any) for qPCR testing of talimogene laherparepvec DNA.
- Radiographic and clinical tumor assessment
- Reporting disease related events, adverse events, serious adverse events and documentation of concomitant medications
- Reporting potential or known unintended exposure to talimogene laherparepvec as specified in Section 9.4

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, talimogene laherparepvec-related adverse events, and initiation of additional anti-tumor treatment. For subjects in the combination treatment cohort, the long-term follow-up starts after the discontinuation of whichever study drug is discontinued last.

For Part 1, contact for all subjects will be attempted approximately every 12 weeks (± 28 days) following the safety follow-up visit until death, subject withdrawal, or up to approximately 24 months after the date of the last subject enrolled in Part 1. Subjects in Cohort 5 and 6 will be followed approximately 24 months after the last subject enrolled in their cohort in Part 1, or approximately 24 months after the last subject enrolled with their tumor type in Part 2, whichever is later.

For Part 2, contact for all subjects will be attempted approximately every 12 weeks (± 28 days) following the safety follow-up visit until death, subject withdrawal, or up to approximately 24 months after the date of the last subject enrolled in that tumor cohort.

Radiographic Tumor Assessment: Every effort should be made to complete radiographic assessments approximately every 12 (+1) weeks during the long-term follow-up until documentation of PD per modified irRC-RECIST (Appendix D), start of new anticancer treatment, death, or end of study, whichever occurs first, for subjects discontinuing treatment for any reason other than PD. Response (CR, or partial response [PR]) or disease progression to be confirmed by second consecutive radiographic assessments no less than 4 weeks from the date of the first documented response or disease progression.

For a full list of study procedures, including the timing of each procedure, please refer to Section 7 and the Schedule of Assessments (Table 8 through Table 13).

Statistical Considerations:

The data will be analyzed by cohort/group (non-HCC and HCC), in the overall population and by tumor type, if applicable. Descriptive statistics will be provided for demographic, safety, efficacy, and biomarkers as appropriate. Formal analysis will be performed on the primary endpoints in Part 2.

For Part 1, the DLT analysis set will be used to summarize the subject incidence of DLT as defined in Section 3.1.4.3. For talimogene laherparepvec monotherapy, safety will be assessed for non-HCC and HCC groups based on the 3 + 3 design. For the combination of talimogene laherparepvec with pembrolizumab, safety will be assessed for non-HCC and HCC groups based on the mTPI up-and-down design. The DLRT will consider prospective guidelines in the DLRT Charter to monitor safety in Part 2 separately by tumor type and, if introduced, talimogene laherparepvec total volumes > 4 mL within Group A and Group B as discussed in Section 10. If the concentration is reduced in Part 2 for a tumor type, then the sample size considerations for the 2-stage futility and efficacy analyses of that tumor type will include only subjects treated in Part 1 and 2 at the reduced concentration.

Objective response rate, BOR, DRR, DOR, response in injected and uninjected lesions, DCR, PFS, and OS will be summarized separately for non-HCC and HCC tumors in monotherapy and combination cohorts. Objective response rate, DRR, and DCR will be summarized with an associated 95% CI.

For Part 2, the efficacy analysis will be conducted using the full analysis set from Part 2, unless otherwise specified. The primary analysis of efficacy will include subjects that receive any volume of talimogene laherparepvec (in monotherapy cohorts) or any volume of talimogene laherparepvec and pembrolizumab (in combination cohorts). The 2-stage design will be used to evaluate the ORR per the modified irRC-RECIST. The null hypothesis of a 10% ORR for a given tumor type that continued to Stage 2 will be rejected if an exact binomial 95% CI for the ORR is above 10% (Atkinson and Brown, 1985).

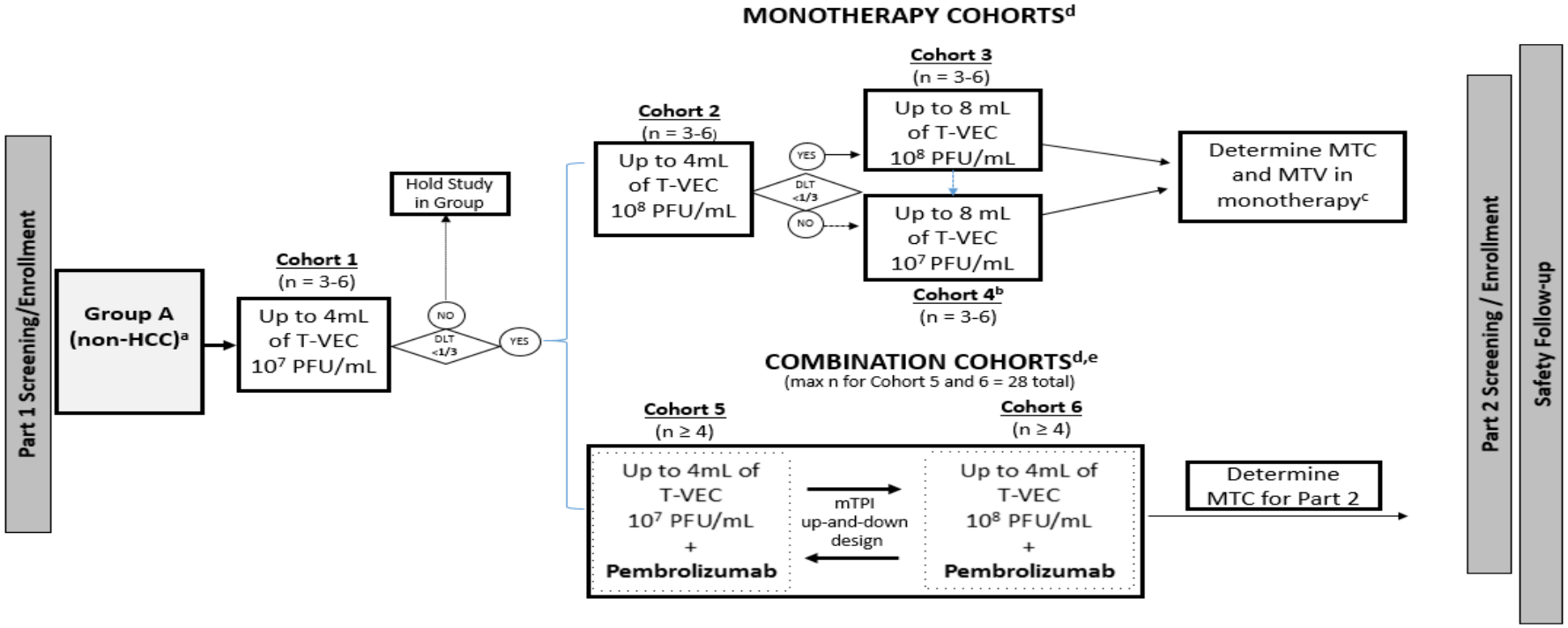
Best overall response, DRR, DOR, response in injected and uninjected lesions, DCR, PFS, and OS will be summarized by primary tumor type arm (hormone receptor positive BC, TNBC, CSCC, CRC, BCC, and HCC with and without viral hepatitis). Objective response rate, DRR, and DCR will be summarized with an associated 95% CI. Duration of response among responders, PFS and OS will be estimated using the Kaplan-Meier method.

For both Part 1 and Part 2, the safety analysis set will be used for all safety analyses. The safety analyses will include the incidence of treatment-emergent and treatment-related adverse events (all adverse events, ≥ grade 3 adverse events, serious adverse events, fatal adverse events and adverse events defined as events of interest). 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. Interim safety analyses will be performed for evaluation of DLT for Parts 1 and 2 for DLRT meetings. All available Part 1 and 2 safety data from both Group A and B will be considered at each interim safety analysis. At the discretion of the DLRT, additional safety analyses may be conducted. For a full description of statistical analysis methods, please refer to Section 10.

Sponsor: Amgen, Inc.

Data Element Standards Version/Date:	Version 4.0, 31 October 2013

Study Design and Treatment Schema: Part 1 - Group A



DLT = dose-limiting toxicity; HCC = hepatocellular carcinoma; MTC = maximum tolerated concentration; mTPI = modified Toxicity Probability Interval; MTV = maximum tolerated volume; PFU = plaque forming unit; T-VEC = talimogene laherparepvec

[a] First dose concentration of talimogene laherparepvec is always 10^6 PFU/mL

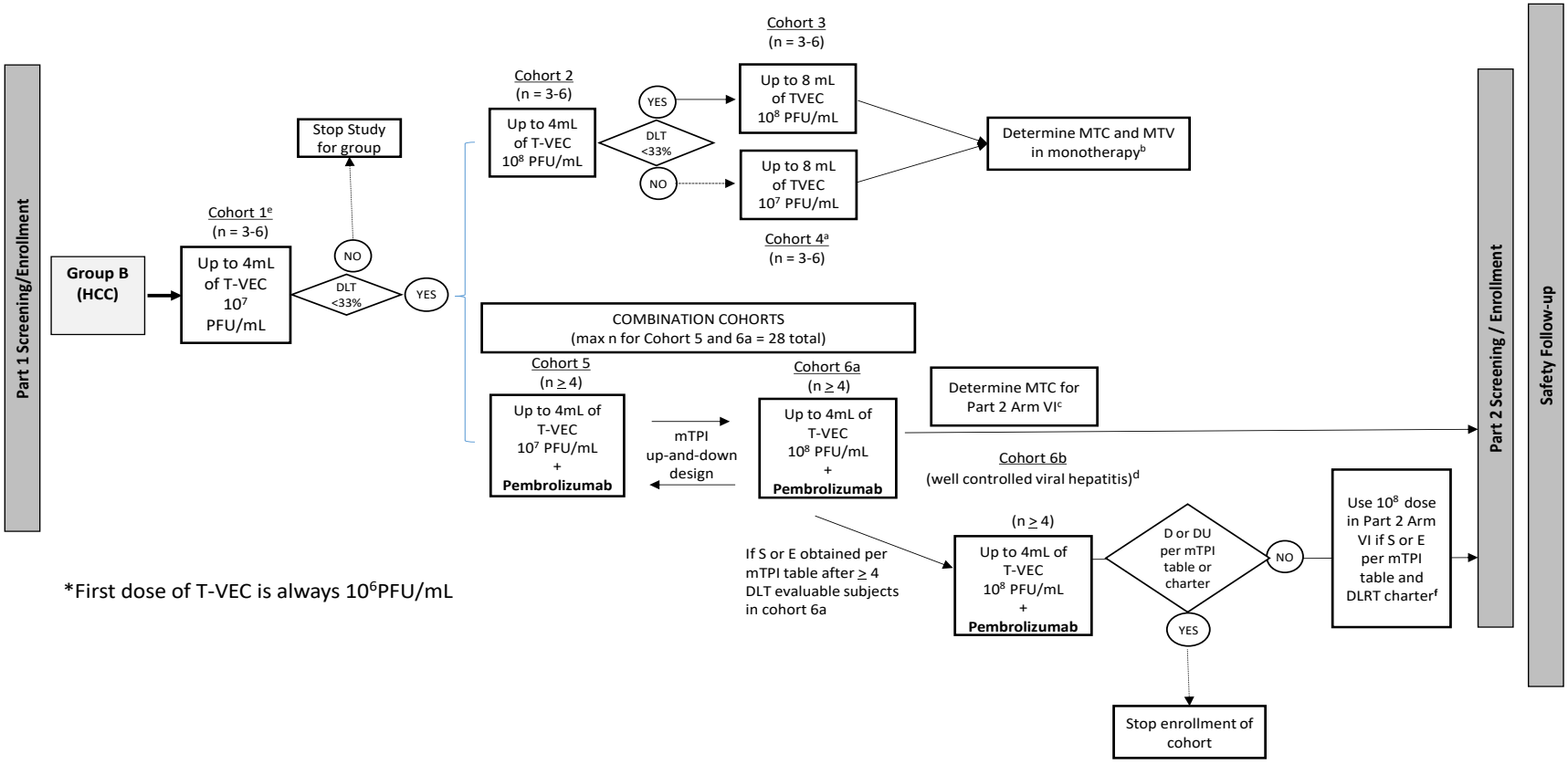
[b] Cohort 4 will be opened only if one of these conditions are met: 1) DLT rate ≥ 1/3 in Cohort 2, or 2) DLT rate ≥ 1/3 in Cohort 3 and Part 2 dose for talimogene laherparepvec not determined yet, or 3) DLT rate ≥ 1/3 in cohort 3 and Part 2 concentration for talimogene laherparepvec is determined to be 10^7 PFU/mL

[c] MTV determined from monotherapy cohorts, when available, may be used in Part 2

[d] If both Cohorts 3 or 4 and the combination Cohorts (5 or 6) are open in the same institution, subjects with a tumor burden who can receive 8 mL (see Section 6.2.1) enrollment into Cohorts 3 or 4 must be strongly preferred until the MTV in monotherapy is determined.

[e] Refer to Section 3.1.4.2 and Table 17 for mTPI dose decision outcomes

Study Design and Treatment Schema: Part 1 - Group B

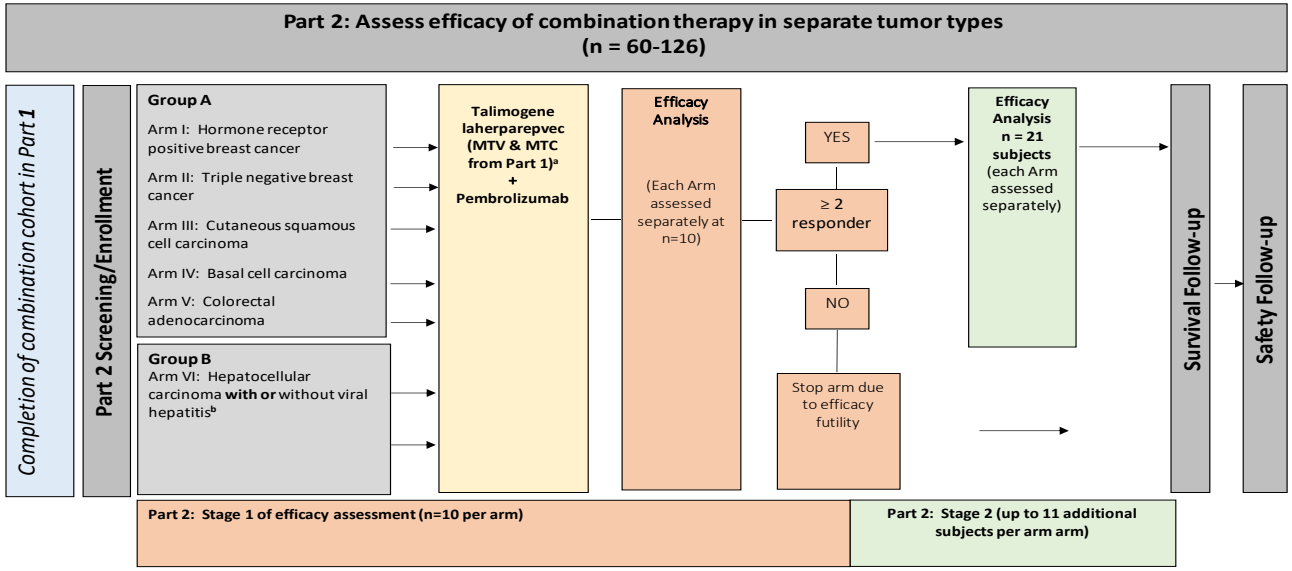


Footnotes defined on next page

D = de-escalate to the next lower dose; DLT = dose-limiting toxicity; DU = de-escalate to the next lower dose/the current dose is unacceptably toxic; E = escalate; HCC = hepatocellular carcinoma; MTC = maximum tolerated concentration; mTPI = modified Toxicity Probability Interval; MTV = maximum tolerated volume; PFU = plaque forming unit; S = stay at current dose; T-VEC = talimogene laherparepvec

[a] Cohort 4 will be opened only if cohort 3 talimogene laherparepvec dose was 10^8 and 1) DLT>33% in Cohort 3 and Part 2 dose for talimogene laherparepvec not determined yet or 2) DLT > 33% in cohort 3 and Part 2 dose for TVEC is determined to be 10^7 PFU/mL
[b] MTV determined from monotherapy cohorts, when available, may be used in Part 2 depending on TVEC combination dose determined for Part 2 from Cohort 5 and 6.
[c] If cohort 6b completes prior to cohorts 5 and 6a mTPI dose finding is completed, and 6b is deemed safe, then cohorts 5 and 6a will close to enrollment and the cohort 6b dose will be used for Arm VI in Part 2.
[d] Cohorts 1-5 and 6a will consist of subjects without viral hepatitis whereas Cohort 6b will consist of subjects with well-controlled viral hepatitis.
[e] Cohort 1 of Group B will be initiated only after safety has been established in Cohort 1 of Group A.
[f] If either Cohort 6a or Cohort 6b in Group B of Part 1 is deemed unsafe to move to Part 2, then only the cohort that is deemed safe will be enrolled in Arm VI in Part 2.

Study Design and Treatment Schema – Part 2



MTC = maximum tolerated concentration; MTV = maximum tolerated volume.
[a] May increase up to 8 ml after safety shown in Cohort 3 or 4 in Part 1.
[b] If either Cohort 6a or Cohort 6b in Group B of Part 1 is deemed unsafe to move to Part 2, then only the cohort that is deemed safe will be enrolled in Arm VI in Part 2.

Study Glossary

Abbreviation or Term	Definition/Explanation
AFP	alpha fetoprotein
ANC	absolute neutrophil count
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ALP	alkaline phosphatase
AST	aspartate aminotransferase
BC	breast adenocarcinoma
BCC	basal cell carcinoma
BOR	best overall response
BRAF	B-Raf sarcoma viral oncogene homolog
BUN	blood urea nitrogen
CA 19-9	cancer antigen 19-9
CD	cluster of differentiation
CEA	carcinoembryonic antigen
CI	confidence interval
CNS	central nervous system
Cohort	both Group A and B consists of cohorts that enroll DLT-evaluable subjects administering a maximum of 4 mL or 8 mL talimogene laherparepvec with or without pembrolizumab
CR	complete response
CRC	colorectal adenocarcinoma
CRF	case report form
CRO	contact research organization
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CSCC	cutaneous squamous cell carcinoma
CZ	Crystal Zenith
D	de-escalate to the next lower dose
DCR	disease control rate
DILI	drug-induced liver injury
DLRT	Dose Level Review Team
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
DRR	durable response rate
DU	de-escalate to the next lower dose/the current dose is unacceptably toxic

Abbreviation or Term	Definition/Explanation
EDC	electronic data capture
ECG	electrocardiogram
ECI	events of clinical interest
ECOG	Eastern Cooperative Oncology Group
End of Follow-up	defined as when the last subject completes the last protocol-specified assessment in the study
End of Study for Individual Subject	defined as the last day that protocol-specified procedures are conducted for an individual subject
End of Study (primary completion)	defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoints, whether the study concluded as planned in the protocol or was terminated early. The primary completion date is the date when all subjects (Parts 1 and 2) have a minimum potential follow-up of ≥ 29 weeks. 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 (end of trial)	defined as the date when the last subject 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. The end of study will occur when the last subject discontinues talimogene laherparepvec and/or pembrolizumab (whichever is later) and has had the opportunity to complete both the safety follow-up visit and the long-term survival follow-up.
End of Treatment	defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject
ER	estrogen receptor
FISH	fluorescence in situ hybridization
FSH	follicle stimulating hormone
FT3	free triiodothyronine
FT4	free thyroxine
GCP	Good Clinical Practice
GEC	gastroesophageal cancer (adenocarcinoma or squamous cell carcinoma)
GM-CSF	granulocyte-macrophage colony-stimulating factor
Group A Part 1	subjects with non-hepatocellular carcinoma (BC, CRC, GEC, melanoma, NSCLC, or RCC) with liver metastases
Group A Part 2	subjects with non-hepatocellular carcinoma (BC, CRC, CSCC, BCC) with or without liver metastases
Group B	subjects with hepatocellular carcinoma with and without well-controlled viral hepatitis
H0	null hypothesis
H1	alternative hypothesis
HBV	hepatitis B virus

Abbreviation or Term	Definition/Explanation
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDV	hepatitis D virus
HepBcAb	total Hepatitis B Core Antibody
HepBsAg	Hepatitis B Surface Antigen
HIV	human immunodeficiency virus
HR	hazard ratio
HRT	hormonal replacement therapy
HSV-1	herpes simplex virus type 1
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	independent ethics committee
IFNg	interferon gamma
Ig	immunoglobulin
IgC	immunoglobulin constant-type
IgG	immunoglobulin G
IgG4	immunoglobulin G4
IgV	immunoglobulin variable-type
IHC	immunohistochemistry
INR	international normalization ratio
Interactive Voice Response (IVR)	telecommunication technology that is linked to a central computer in real time as an interface to collect and process information
IPIM	Investigational Product Instruction Manual
IRB	institutional review board
irRC-RECIST	immune-related response criteria (irRC) simulating RECIST version 1.1
IT	intratumorally
ITSM	immunoreceptor tyrosine-based switch motif
IV	intravenous
JX-594	pexastimogene devacirepvec (Pexa-Vec)
KRAS	Kristen rat sarcoma viral oncogene homolog
LDH	lactate dehydrogenase
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MHC	major histocompatibility complex class
MRI	magnetic resonance imaging
MTC	maximum tolerated concentration
MTD	maximum tolerated dose

Abbreviation or Term	Definition/Explanation
mTPI	modified toxicity probability interval mTPI Outcomes: E = Escalate to the next higher dose S = Stay at the current dose D = De-escalate to the next lower dose U = The current dose is unacceptably toxic
MTV	maximum tolerated volume
NK	natural killer cells
non-HCC	metastatic liver tumors (if tumors are present in liver)
NRAS	neuroblastoma RAS viral oncogene homolog
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
Part 1	Part 1 is a dose escalation study to evaluate the safety of intrahepatic injection of talimogene laherparepvec into liver tumors alone and in combination with systemic IV administration of pembrolizumab
Part 2	Part 2 is a 2-stage design to evaluate the efficacy of talimogene laherparepvec in combination with systemic pembrolizumab
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed cell death 1
PD-L1 or 2	programmed cell death ligand 1 or 2
PET	positron emission tomography
PFS	progression-free survival
PFU	plaque forming unit
PK	pharmacokinetics
POR	proof of receipts
PR	partial response
PrR	progesterone receptor
PT	prothrombin time
PTT/aPTT	partial thromboplastin time/activated PTT
Q2W	every 2 weeks
Q3W	every 3 weeks
Q21D	every 21 days
qPCR	real-time polymerase chain reaction
RBC	red blood cell
RCC	clear cell renal cell carcinoma
RP2D	recommended phase 2 dose
RT-PCR	reverse transcriptase by polymerase chain reaction
RECIST	Response Evaluation Criteria in Solid Tumors
SCC	squamous cell carcinoma

Abbreviation or Term	Definition/Explanation
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.
SD	stable disease
SOC	system organ class
Study Day 1	defined as the first day that protocol-specified investigational product is administered to the subject
T3	triiodothyronine
TBL	total bilirubin
TCID50	50% Tissue Culture Infective Dose
tk	thymidine kinase
TEAE	treatment-emergent adverse event is an event that emerges during treatment, having been absent pretreatment, or worsens relative to the pretreatment state
TNBC	triple negative breast cancer
TRAE	treatment-related adverse events is a TEAE that is suspected to be related to the study treatment
TSH	thyroid-stimulating hormone
T-VEC	talimogene laherparepvec
ULN	upper limit of normal
US	ultrasound
USA	United States of America
WBC	white blood cell

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1. OBJECTIVES

1.1 Primary

Part 1 (NOTE: as of Protocol Amendment 6 [dated 26 October 2021], intrahepatic injections of talimogene laherparepvec and liver biopsies are no longer performed in this study):

To evaluate the following, as assessed by the incidence of dose-limiting toxicities (DLTs) in subjects with liver metastases (non-HCC) and subjects with primary hepatocellular carcinoma (HCC) in:

- Monotherapy Cohorts: the maximum tolerated volume and concentration (MTV and MTC) of intrahepatic injection of talimogene laherparepvec into liver tumors in subjects with non-HCC and subjects with primary HCC without active viral hepatitis
- Combination Cohorts: the MTC of intrahepatic injection of talimogene laherparepvec into liver tumors in combination with systemic intravenous (IV) administration of pembrolizumab in subjects with non-HCC, and subjects with primary HCC with or without viral hepatitis

Part 2:

- To evaluate the efficacy, as assessed by objective response rate (ORR) of intratumoral injection of talimogene laherparepvec in combination with systemic IV administration of pembrolizumab, separately, for each non-HCC tumor type (hormone receptor positive breast adenocarcinoma [BC], triple negative breast cancer [TNBC], colorectal adenocarcinoma [CRC], cutaneous squamous cell carcinoma (CSCC)], basal cell carcinoma [BCC], as well as primary HCC with and without viral hepatitis
- To evaluate safety separately for each tumor type as assessed by subject incidence of treatment-emergent and treatment-related adverse events, including DLTs

1.2 Secondary

The secondary objectives of the study are as follows:

Efficacy

Part 1:

- To evaluate the efficacy separately by monotherapy versus combination for non-HCC and HCC with and without viral hepatitis when applicable as assessed by:
  - ORR, best overall response (BOR), durable response rate (DRR), duration of response (DOR), response in injected and uninjected lesions, disease control rate (DCR), progression-free survival (PFS), and overall survival (OS)

Part 2:

- To evaluate the efficacy in individual tumor types in the non-HCC group and HCC group with and without viral hepatitis as assessed by:

- BOR, DRR, DOR, response in injected and uninjected lesions, DCR, PFS, and OS by primary tumor type arm (TNBC, Hormone receptor positive BC, CRC CSCC, BCC, and HCC with and without viral hepatitis)

Safety (Parts 1 and 2)

- To evaluate the safety in each monotherapy and combination cohorts in Part 1 and each arm separately in Part 2, as assessed by subject incidence of treatment-emergent and treatment-related adverse events
- To estimate the incidence of detectable talimogene laherparepvec deoxyribonucleic acid (DNA) in blood and urine
- To estimate the incidence of clearance of talimogene laherparepvec DNA from blood and urine
- To estimate the rate of detection (per sample) and incidence (per subject) of talimogene laherparepvec DNA and virus at the surface of talimogene laherparepvec injection site, the exterior of the occlusive dressing, and the oral mucosa
- To estimate the incidence of talimogene laherparepvec DNA detection in lesions suspected to be herpetic in origin

1.3 Exploratory

The exploratory objectives of the study are as follows:

[redacted]

2. BACKGROUND AND RATIONALE

2.1 Hepatocellular Carcinoma and Metastatic Liver Tumors

In addition to being the organ of origin for HCC, the liver is one of the major sites of metastasis for many tumor types. In autopsy studies, the incidence of liver metastases was 48.6 to 61.1% for breast cancer, 33.4 to 40% for lung cancer, 34.3 to 44.5% for gastric cancer, 65.3% for colon cancer, 33.3 to 47.1% for rectal cancer, 16 to 27% for kidney cancer (Abrams et al, 1950), and 58.3% for melanoma (Patel et al, 1978). Metastasectomy is an option for limited CRC liver metastases, but generally systemic therapies such as chemotherapy are the primary modality of treatment for most cancers which have metastasized to the liver. Traditionally, melanoma and RCC are thought to be the most sensitive tumor types to immunotherapy, but recent advances in immune checkpoint blockade therapies have suggested benefit of immunotherapy in other tumor types as well (eg, NSCLC) (Nguyen et al, 2014).

Localized HCC is primarily treated by surgery, transplant or locally ablative therapies. Resection of HCC is generally reserved for those patients with limited disease. Other localized therapies against liver tumors may include bland embolization, transarterial

chemoembolization, transarterial radioembolization, radiofrequency ablation, laser and microwave ablation, cryoablation, or percutaneous ethanol injection and are more commonly used in the setting of unresectable HCC but may also be used in the setting of liver metastases. The currently FDA-approved systemic therapies for unresectable or metastatic HCC are the small molecule multi-kinase inhibitors sorafenib (for treatment unresectable HCC) (Llovet et al, 2008), lenvatinib (for first line treatment of unresectable HCC) (Kudo et al, 2018) and regorafenib (for those previously treated with sorafenib) (Bruix et al, 2017), and cabozantinib (for those previously treated with sorafenib) (Abou-Alfa et al, 2018) and accelerated approval for the PD-1 inhibitors nivolumab (for those previously treated with sorafenib)
(El-Khoueiry, et al, 2017) and pembrolizumab (for those previously treated with sorafenib) (Zhu et al, 2018) and the monoclonal antibody ramicirumab (for patients with alpha fetal protein >400 ng/ml who were previously treated with sorafenib) (Zhu, et al, 2019). Of note, the phase 3 KEYNOTE-240 trial evaluating pembrolizumab plus best supportive care compared to placebo plus best supportive care for the treatment of patients with advanced HCC previously treated with systemic therapy did not meet its co-primary endpoints of improved overall survival and progression free survival. While the numbers numerically favored the pembrolizumab plus best supportive care arm, they did not reach statistical significance (Finn, et al, 2019).

Even with the currently available treatment options, unresectable HCC and metastases of other solid tumors to the liver generally portend a poor prognosis, and thus, new therapies are urgently needed for these patients.

2.2 Oncolytic Virus Studies with Intrahepatic Administration

The safety and activity of oncolytic viruses has been studied against various tumor types in the liver. JX-594 (pexastimogene devacirepvec [Pexa-Vec]) is a modified vaccinia virus with a disrupted thymidine kinase (tk) gene to improve selectivity for cancer and insertions of human granulocyte-macrophage colony-stimulating factor (GM-CSF) for immune stimulation and β-galactosidase for assessment of replication. It was administered intratumorally (IT) in a phase 1 trial to 14 subjects with primary HCC or non-HCC in a dose escalation study (Park et al, 2008). DLT occurred at the highest dose of 3×10^9 plaque forming unit (PFU) with grade 3 hyperbilirubinemia due to obstruction of the intrahepatic bile duct by the injected tumor and grade 3 anorexia and abdominal pain, which was a serious adverse event. Thus, 10^9 PFU was determined as the maximum tolerated dose (MTD). No treatment-related deaths occurred. All subjects

had grade 1 to 2 flu-like symptoms. Of 10 evaluable subjects, 3 had partial responses (PRs) (lung SCC, HCC, and melanoma), and 6 had stable disease (SD) by Response Evaluation Criteria in Solid Tumors (RECIST). By Choi response criteria, an additional 5 subjects with SD by RECIST were found to also have a PR (CRC, 2 subjects and RCC, thymic SCC, and extragonadal germ cell tumor, 1 subject each). In a subsequent dose-finding phase 2 study, 30 subjects with advanced HCC were randomized to either 10^8 or 10^9 PFU JX-594 injected IT into up to five HCC tumors on days 1, 15, and 29 (Heo et al, 2013). Treatment was generally well tolerated at both doses, and there were no treatment-related deaths. There was one treatment-related serious adverse event of nausea and vomiting at the 10^9 PFU dose. Grade 1 to 2 flu-like symptoms occurred in all subjects in the first 12 to 24 hours after treatment. The only grade 3 event was pyrexia which occurred in 19% of subjects treated at the 10^9 PFU dose and one grade 4 event of lymphopenia occurred at the 10^9 PFU dose. The trial was stopped early due to significant survival benefit favoring the higher-dose group (14.1 months vs 6.7 months) with median OS at 9.0 months for the entire study population. There was no significant difference, however, in either modified RECIST or modified Choi responses between the higher and lower dose (7% vs 23% and 57% vs 67%, respectively). A subsequent phase 2b study evaluating JX-594 for 6 treatments on days 1 (IV), 8 (IT), 22 (IT), and weeks 6 (IT), 12 (IT), 18 (IT) vs best supportive care in 120 second-line advanced subjects with HCC refractory or intolerant to sorafenib did not meet its primary endpoint of OS (Transgene, 2013). However, a pivotal phase 3 study evaluating sorafenib with or without JX-594 in the first line setting for approximately 600 subjects with HCC is ongoing (United States National Institutes of Health, 2016; Transgene, 2014).

NV1020, an attenuated derivative of herpes simplex virus type 1 (HSV-1) that has deletions of the genes encoding ICP34.5, UL56, UL24, and tk and reinsertion of a functional HSV-1 tk gene, was administered into the liver intra-arterially for unresectable CRC liver metastases in a phase 1/2 study (Geevarghese et al, 2010). Doses from 3×10^6 to 1×10^8 PFU were administered for up to four infusions to 13 subjects in the dose-escalation phase 1 portion, and no DLTs were seen. For phase 2, the 1×10^8 PFU dose was administered to 19 subjects. The most common adverse events were transient chills, headache, nausea, vomiting, myalgia, body pains, and fatigue. No treatment-related disturbances in liver function were seen. An asymptomatic grade 3 lymphopenia occurred after infusions in 1 subject. At the 1×10^8 PFU dose, 1 PR and

13 SD were seen in 22 evaluable subjects. Mean time to progression was 6.4 months, and mean OS was 11.8 months at the highest treatment dose.

2.3 Talimogene Laherparepvec Investigational Product Background

Talimogene laherparepvec is an intralesionally delivered oncolytic immunotherapy comprised of a genetically engineered HSV-1 that selectively replicates in tumors (Talimogene Laherparepvec Investigator's Brochure **[IB]**). The neurovirulence factor ICP34.5 and the ICP47-encoding gene from HSV-1 are functionally deleted in talimogene laherparepvec, while the gene for GM-CSF is inserted. The ICP34.5 functional deletion allows the virus to replicate selectively in tumors over normal tissue. Normal cells have intact antiviral response pathways to which the HSV-1 protein ICP34.5 confers resistance. Because talimogene laherparepvec lacks ICP34.5, it cannot replicate as effectively in normal cells as wild type HSV-1. However, in many cancer cells, the antiviral response pathway is dysregulated and permits talimogene laherparepvec replication eventually leading to oncolysis. The oncolytic activity of talimogene laherparepvec has been demonstrated either in vitro or in vivo against a number of different solid tumor types including BC, CRC, prostate cancer, glioblastoma, hypopharyngeal SCC, and melanoma cell lines (Liu et al, 2003). The role of ICP47 is to block antigen presentation to major histocompatibility complex class (MHC) I molecules by blocking the transporter associated with antigen processing 1 and 2. Deletion of ICP47 allows for improved antigen presentation by MHC molecules and 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 by promoting the generation of dendritic cells from blood monocytes (Demir et al, 2003; Lonial, 2004; Conti and Gessani, 2008). Dendritic cells have the capacity to capture antigens, migrate in response to chemotactic stimuli, and induce proliferative responses and Th1 cytokine production in cluster of differentiation 4 (CD4+) and CD8+ T-lymphocytes (Hart, 1997; Ikeda et al, 2004; Paul, 2007). These Th1-type cytokines have the capacity to produce proinflammatory responses, eradicate tumors, and perpetuate autoimmune responses (Nishimura et al, 2000; Ikeda et al, 2004; Knutson and Disis, 2005). This immune component of talimogene laherparepvec is thought to help mediate systemic responses beyond the injected tumors.

Talimogene laherparepvec has clinical efficacy in patients with regionally and distantly metastatic melanoma (Talimogene Laherparepvec **IB**). In the melanoma setting, talimogene laherparepvec has been administered into cutaneous or subcutaneous lesions or lymph nodes accessible by ultrasound (US) but not yet into visceral lesions. The largest study to evaluate the activity of talimogene laherparepvec in melanoma was the pivotal OPTiM study (Study 20110263). In this open-label, phase 3 study, 436 subjects with stages IIIB to IV unresectable melanoma were randomized 2:1 to intralesional talimogene laherparepvec or subcutaneous GM-CSF. Treatment was administered until complete response (CR), clinically significant disease progression, intolerable side effects, 12 months of therapy without an objective response, or withdrawal of consent). The primary endpoint of the OPTiM study was DRR, defined as the rate of subjects with an objective response by central review (CR or PR) lasting continuously for 6 months and starting any time within 12 months of initiating therapy. Secondary endpoints included OS, BOR, modified PFS, changes in tumor burden and safety.

Primary analysis of the OPTiM study showed a statistically significant difference between the DRR 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). Overall response rate was 26.4% (CR 10.8%) for talimogene laherparepvec vs 5.7% (CR 0.7%) for GM-CSF (p-value < 0.0001 descriptive). Median OS among subjects treated with talimogene laherparepvec was 23.3 months vs 18.9 months among subjects treated with GM-CSF with an OS hazard ratio (HR) of 0.79 and p-value of 0.051 (Andtbacka et al, 2013; Kaufman et al, 2014).

In a lesion level analysis, 64% and 47% of injected lesions, 34% and 22% of uninjected non-visceral lesions, and 15% and 9% of uninjected visceral lesions regressed $\geq$ 50% and 100%, respectively, demonstrating the systemic effect of talimogene laherparepvec beyond injected lesions (Andtbacka et al, 2014).

The most common side effects in the OPTiM study were chills (talimogene laherparepvec, 49%; GM-CSF, 9%), pyrexia (43%; 9%), injection-site pain (28%; 6%), nausea (36%; 20%), influenza-like illness (30%; 15%), and fatigue (50%; 36%). Grade $\geq$ 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 $\geq$ 5 subjects was cellulitis (talimogene laherparepvec, n=6 [2.1%];

GM-CSF, n=1 [<1%]). Of 10 fatal adverse events in the talimogene laherparepvec arm, eight were attributable to disease progression. The remaining two fatal adverse events (sepsis in the setting of salmonella infection; myocardial infarction) were not considered treatment-related per investigator (Andtbacka et al, 2013).

The injection of talimogene laherparepvec into visceral tumors has been studied in the 005/04 phase 1 study for pancreatic cancer in subjects who either failed standard therapy or could not receive/refused alternative therapy (Chang et al, 2012). There were 17 subjects who received endoscopic US guided injections into their pancreatic tumors at either 1 dose of 10^4 PFU/mL followed by 2 doses of 10^5 PFU/mL every 3 weeks (Q3W; Cohort 1, n=3), 1 dose of 10^5 PFU/mL followed by 2 doses of 10^6 PFU/mL Q3W (Cohort 2, n=4), or 1 dose of 10^6 PFU/mL followed by 2 doses of 10^7 PFU/mL Q3W (Cohort 3, n=10). A fourth dose schedule of 10^6 PFU/mL followed by 2 doses of 10^8 PFU/mL Q3W was planned but not opened because the study was terminated early due to a business decision. The maximal volume that could be administered was 4 mL.

The primary analysis of efficacy was an assessment of the change from baseline in the diameter of injected tumors. Two of the 4 subjects in Cohort 3 with postdose computed tomography (CT) scans achieved substantial size reductions (-36% and -33%) in injected tumors. No subjects in the lower dose cohorts (n = 2 evaluable subjects in each cohort) showed clinically relevant size reductions of the injected tumors, suggesting a dose trend for response of injected tumors. Three subjects also showed decreases in the diameters of 1 or more uninjected tumors (in the liver, pancreas, kidney, and chest) at any point in the study, and 1 subject had complete disappearance of a non-measurable tumor in the liver. A dose trend was not observed for size reductions of uninjected tumors. In the evaluation of overall tumor burden per RECIST version 1.0, no subjects achieved an overall CR or PR; 3 subjects (Cohorts 1, 1, and 3) had an assessment of overall SD at 1 or more time points.

Eight subjects (47%) had at least 1 treatment-emergent adverse event considered related to talimogene laherparepvec. Treatment-related adverse events included pyrexia in 3 subjects; abdominal pain, ascites, influenza-like illness, and dehydration in 2 subjects; and constipation, vomiting, chills, pain, headache, weight decrease, and diarrhea in 1 subject each. Grade 3 treatment-related adverse events included abdominal pain (12%), ascites (12%), and dehydration (6%); all occurred in Cohort 3. Eleven deaths were reported, mostly due to pancreatic cancer-related complications.

One subject with a fatal outcome had an adverse event of ascites considered possibly related to study treatment by the investigator. This subject was hospitalized for severe ascites 1 week after the first dose of talimogene laherparepvec, and later experienced disease progression and received home hospice care; the event of ascites was ongoing at the time of the subject's death approximately 1 month later.

Prior to initiating enrollment of this study, no injections of hepatic tumors in humans have been attempted with talimogene laherparepvec. However, the hepatotoxicity of talimogene laherparepvec administration in the liver has been evaluated in immunocompetent rats. Up to 10^7 PFU of talimogene laherparepvec per animal or vehicle was administered via intrahepatic artery injection. No differences in morbidity or mortality were noted between talimogene laherparepvec and vehicle treated groups (Data on file).

Refer to the Talimogene Laherparepvec **IB**, for additional information.

2.4 Non-Amgen Investigational Product: Pembrolizumab Background

2.4.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades (Disis, 2010). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and prognosis in various malignancies (Mei et al, 2014; Salgado et al, 2014; Schatton et al, 2014; Bremnes et al, 2011; Gooden et al, 2011; Schreiber et al, 2011; Talmadge, 2011; Nosho et al, 2010; Shirabe et al, 2010; Bellati et al, 2009; Oble et al, 2009; Uppaluri et al, 2008; Dunn et al, 2007). In particular, the presence of CD8+ T cells and the ratio of CD8+ effector T cells/FoxP3+ regulatory T cells seem to correlate with improved prognosis and long-term survival in many solid tumors (Chang et al, 2014; Kim et al, 2013; Preston et al, 2013; Mathai et al, 2012; Yoon et al, 2012; Liu et al, 2011; Kirk, 2010; Nosho et al, 2010).

The programmed cell death-1 (PD-1) receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control (Pedoeem et al, 2014). The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an immunoglobulin (Ig) superfamily member related to CD28 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). The structures of murine PD-1 alone

(Zhang et al, 2004) and in complex with its ligands were first resolved (Lázár-Molnár et al, 2008; Lin et al, 2008), and more recently the nuclear magnetic resonance-based structure of the human PD-1 extracellular region and analyses of its interactions with its ligands were also reported (Cheng et al, 2013). PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (IgV) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif and an immunoreceptor tyrosine-based switch motif (ITSM). Following T cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules, such as cluster of differentiation 3-zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase 70 (ZAP70), which are involved in the CD3 T cell signaling cascade (Sheppard et al, 2004). The mechanism by which PD-1 down-modulates T cell responses is similar to, but distinct from that of CTLA-4 (Ott et al, 2013). PD-1 was shown to be expressed on activated lymphocytes, including peripheral CD4+ and CD8+ T cells, B cells, T regs and Natural Killer cells (Yao and Chen, 2014). Expression has also been shown during thymic development on CD4-CD8- (double negative) T cells (Nishimura et al, 1996), as well as subsets of macrophages (Huang et al, 2009) and dendritic cells (Pena-Cruz et al, 2010). The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types (Keir et al, 2008). PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments (Keir et al, 2008). Both ligands are type I transmembrane receptors containing both IgV- and immunoglobulin constant-type (IgC)-like domains in the extracellular region and short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T cell activation triggered through the T cell receptor. PD-L2 is thought to control immune T cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T cell inhibitor (Taube et al, 2012; Karim et al, 2009), which, via its interaction with the PD-1 receptor on tumor-specific T cells, plays a critical role in immune evasion by tumors (Sanmamed and Chen, 2014). As a consequence, the

PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in cancer (Topalian et al, 2012).

2.4.2 Pre-clinical Studies

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T cells and ultimately leads to tumor rejection, either as a monotherapy or in combination with other treatment modalities (Spranger et al, 2014; Curran et al, 2010; Pilon-Thomas et al, 2010; Weber, 2010; Hirano et al, 2005; Blank et al, 2004; Strome et al, 2003). Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated antitumor responses in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, acute myeloid leukemia and colorectal carcinoma (Curran et al, 2010; Pilon-Thomas et al, 2010; Zhang et al, 2009; Nomi et al, 2007; Strome et al, 2003). In such studies, tumor infiltration by CD8+ T cells and increased IFNg, granzyme B and perforin expression were observed, indicating that the mechanism underlying the antitumor activity of PD-1 checkpoint inhibition involved local infiltration and activation of effector T cell function *in vivo* (Curran et al, 2010). Experiments have confirmed the *in vivo* efficacy of anti-mouse PD-1 antibody as a monotherapy, as well as in combination with chemotherapy, in syngeneic mouse tumor models (see the IB).

2.4.3 Pembrolizumab Background and Clinical Trials

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 IV 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 IB (Pembrolizumab **IB**).

2.4.4 Rationale for Pembrolizumab Dose Selection

The dose of pembrolizumab planned to be studied in this trial is 200 mg Q3W. The dose recently approved in the United States and several other countries for treatment of melanoma subjects is 2 mg/kg Q3W. Information on the rationale for selecting 200 mg Q3W is summarized below.

In KEYNOTE-001, 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, 3, and 10 mg/kg, administered every 2 weeks (Q2W) and dose expansion cohorts evaluated 2 mg/kg Q3W and 10 mg/kg Q3W in subjects with advanced solid tumors. All dose levels were well tolerated and no DLTs 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 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 mAbs, 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, 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.

2.5 Rationale

Based on the safety profile of other oncolytic viruses administered into the tumors of the liver and the safety profile of talimogene laherparepvec to date, it is hypothesized that talimogene laherparepvec injected intrahepatically into liver tumors will be tolerable and safe. It is also hypothesized that intrahepatic injection of talimogene laherparepvec into liver tumors will provide control of injected and uninjected hepatic lesions, and uninjected non-hepatic lesions, in subjects with unresectable HCC or liver metastases. The local oncolytic effect of talimogene laherparepvec, as well as its systemic effects through stimulation of an anti-tumor immune response, may provide an alternative approach over purely localized therapies such as liver resection and traditional interventional radiology techniques. A favorable toxicity profile could support further clinical investigation of combination therapy of intrahepatic tumor injections of talimogene laherparepvec with other immunotherapies such as immune checkpoint inhibitors, which overcome signals that might be inhibiting anti-tumor T cells and could potentially enhance the activity of tumor antigen-specific T cells cross-primed by talimogene laherparepvec. On-treatment biomarker studies evaluating biologic or immunologic changes in blood or liver tumor biopsies may provide additional insights on how intrahepatic talimogene laherparepvec treatment might be further optimized in the future.

Thus far in this study, as of a data cutoff of 7 August 2019, subject incidence of treatment-emergent adverse events of any grade that occurred in 20% or more of 26 subjects in the monotherapy cohorts included pyrexia (84.6%), fatigue (46.2%), nausea (30.8%), abdominal pain (38.5%), vomiting (23.1%), headache (30.8%), anemia (26.9%), back pain (23.1%), decreased appetite (23.1%), and dyspnea (23.1%). Treatment emergent treatment related adverse events in the monotherapy cohort that occurred in 10% or more of subjects included pyrexia (80.8%), chills (19.2%), nausea (15.4%), fatigue (19.2%), blood alkaline phosphatase increased (23.1%), headache (26.9%), abdominal pain (19.2%), decreased appetite (11.5%), myalgia (11.5%), procedural pain (11.5%), and anemia (11.5%). Subject incidence of treatment emergent grade $>$ 3

adverse events that occurred in 5% or more in the monotherapy cohort included alanine aminotransferase (ALT) increased (15.4%), anemia (11.5%), aspartate aminotransferase (AST) increased (7.7%), blood alkaline phosphatase increased (7.7%), abdominal pain (7.7%) and hypokalemia (7.7%). Treatment emergent treatment-related serious adverse events included pyrexia (7.7%), abdominal pain (3.8%), ALT increased (3.8%), AST increased (3.8%), blood alkaline phosphatase increased (3.8%), and nausea (3.8%).

As of a data cutoff of 7 August 2019, subject incidence of treatment-emergent adverse events of any grade that occurred in 20% or more of 23 subjects enrolled in the combination cohorts of talimogene laherparepvec and pembrolizumab included pyrexia (87%), fatigue (30.2%), nausea (43.5%, chills (43.5%), vomiting (26.1%), upper abdominal pain (21.7%), diarrhea (26.1%), and AST increased (26.1%). Treatment-emergent treatment-related adverse events related to talimogene laherparepvec included pyrexia (78.3%), chills (30.4%), nausea (30.4%), fatigue (21.7%), AST increased (13.0%), vomiting (13.0%), and hypotension (13.0%). Treatment-emergent treatment related adverse events related to pembrolizumab included pyrexia (39.1%), chills (13.0%), nausea (17.4%), fatigue (26.1%), and AST increased (13.0%). Subject incidence of treatment emergent grade $>$ 3 adverse events that occurred in 5% or more in the combination cohort included ALT increased (8.7%), AST increased (8.7%), blood bilirubin increased (8.7%), and hyponatremia (8.7%). Treatment emergent treatment-related serious adverse events related to talimogene laherparepvec included pyrexia (13.0%), acute kidney injury (4.3%), fatigue (4.3%), and pericarditis (4.3%). Treatment emergent treatment-related serious adverse events related to pembrolizumab included pyrexia (13.0%), acute kidney injury (4.3%), hepatitis cholestatic (4.3%), fatigue (4.3%), and pericarditis (4.3%).

Once safety of intrahepatic injections of talimogene laherparepvec in combination with systemic pembrolizumab is demonstrated in Part I, in Part 2, liver injections as well as injections of other sites previously shown to be safe will be allowed in combination with systemic pembrolizumab to explore efficacy in select solid tumor types.

As of Protocol Amendment 6 (dated 26 October 2021), intrahepatic injections of talimogene laherparepvec and liver biopsies are no longer performed in this study. The risk/benefit evaluation of performing intrahepatic injections of talimogene laherparepvec did not support continued intrahepatic injections (see IB).

2.5.1 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.

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. Talimogene laherparepvec was administered initially with maximum volume of 4 mL at 10^6 PFU/mL. The subsequent doses were administered with maximum volume of 4 mL at 10^8 PFU/mL. 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 1 dose of talimogene laherparepvec. There were no reported DLT during the DLT evaluation period (the 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. There were no unexpected adverse events attributable to the combination therapy that have not been seen previously with either ipilimumab or talimogene laherparepvec individually. Two subjects (11%) experienced possible immune-related grade 3 or 4 adverse events attributed to either ipilimumab or the combination of ipilimumab and talimogene laherparepvec. 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 immune-related response criteria (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. An interim analysis of the phase 2 portion of the study which was performed when 82 patients had ≥ 48 weeks of follow up was reported (Chesney et al, 2016). One-hundred and seventy-three patients were randomized: 88 in the talimogene laherparepvec + ipilimumab arm and 85 in the ipilimumab arm. Characteristics for all patients were similar: 54% stage IIIB-IVM1a, 45% IVM1b/c. Median follow-up time for 82 patients was 61.2 weeks (range: 0.14 to 113.9). Confirmed ORR was 35.7% in the combination arm and 17.5% in the ipilimumab arm with odds ratio for response of 2.6 (95% CI: 0.9 to 7.3). Unconfirmed ORR was 50% in the combination arm and 27.5% in the ipilimumab arm. Safety data in the analysis were as expected based on the phase 1b data; of 165 patients in the safety set (85 in the combination arm and 80 in the ipilimumab arm), the incidences of grade 3/4 treatment related adverse events were similar in both arms (total of 20% in the combination arm and 19% in the ipilimumab arm) with the exception of diarrhea (4% in combination arm vs 0% in ipilimumab arm) and colitis (4% in combination arm vs 8% in ipilimumab arm). A grade 5 autoimmune hepatitis occurred in the combination arm which was attributed to ipilimumab per investigator.

In Study 20110265, a phase 1b/3, multicenter trial of talimogene laherparepvec in combination with pembrolizumab for the treatment of unresectable stage IIIB to IVM1c melanoma, an interim analysis for efficacy of the phase 1b portion of the study was done following minimum of 24 weeks follow-up (data cutoff 09 October 2015). Talimogene laherparepvec was administered initially with maximum volume of 4 mL at 10^6 PFU/mL. The subsequent doses were administered with maximum volume of 4 mL at 10^8 PFU/mL. The confirmed overall response rate was 47% (CR rate, 14%) with a DCR of 71% (Amgen Data on File). The primary analysis of the phase 1b portion of this study has been completed following a minimum of 36 weeks follow up (data cutoff 06 January 2016) and the updated clinical data is now available (Long et al, 2016). Twenty-one subjects received talimogene laherparepvec plus pembrolizumab. Median follow-up was 44 weeks. No DLTs occurred. The most frequent adverse events were fatigue (67%),

fever (52%), chills (48%), and diarrhea (43%). There were no unexpected adverse events attributable to the combination therapy that have not been seen previously with either pembrolizumab or talimogene laherparepvec individually. All patients had ≥ 1 treatment-related adverse event; 6 (29%) were grade 3, and 1 (5%) was grade 4 (pneumonitis). Talimogene laherparepvec-related serious adverse events occurred in 2 (10%) subjects which included grade 1 cytokine release syndrome and grade 3 aseptic meningitis. Pembrolizumab-related serious adverse events occurred in 4 (19%) subjects which included grade 3 autoimmune hepatitis, grade 1 cytokine release syndrome, grade 3 aseptic meningitis, and grade 4 pneumonitis. The confirmed ORR was 57% (CR rate 24%) with a median time to response of 17 weeks. Unconfirmed response rate was 66.7% with a CR rate of 28%. The DCR was 71%. Median PFS was not reached with 71% of patients being progression free at 6 months. Talimogene laherparepvec and pembrolizumab could be administered at full doses with no unexpected toxicity, and was associated with clinical benefits as assessed by ORR and CR rate. Phase 3 portion of the study **was completed 11 March 2021 (IB; Gogas et al, 2021)**.

This phase 1b/2, multicenter study is intended to provide confirmation that a regimen of an oncolytic immunotherapy (intrahepatic injection of talimogene laherparepvec) and an immune checkpoint inhibitor (pembrolizumab) is safe and tolerable, and that the combination treatment might enhance the clinical efficacy shown with anti-PD-1/PD-L1 mAbs in subjects with primary HCC and non- HCC. Given that subjects with HCC may have underlying liver dysfunction compared to subjects with non-HCC primary tumors with liver metastases, this study will determine the feasibility and safety of the initial dose cohort (A1) in the non-HCC group prior to initiating enrollment in cohort B1 in the HCC group. **Following implementation of Protocol Amendment 5 (dated 02 July 2021)**, non-HCC and HCC cohorts will enroll independently after safety is established in the 10^7 PFU/mL monotherapy cohorts.

The safety and efficacy of nivolumab, a PD-1 immune checkpoint inhibitor, was evaluated in CheckMate 040. This phase 1b/2, open-label, non-comparative, dose escalation and expansion trial of nivolumab enrolled adults (≥ 18 years) with histologically confirmed advanced HCC with or without hepatitis C or B virus (H CV or HBV) infection. Previous sorafenib treatment was allowed. In this study, 262 eligible patients were treated (48 patients in the dose-escalation phase and 214 in the dose-expansion phase). Nivolumab had a manageable safety profile and no new signals were observed in patients with advanced HCC. Nivolumab 3 mg/kg was chosen

for dose expansion. The ORR was 20% (95% CI 15–26) in patients treated with nivolumab 3 mg/kg in the dose-expansion phase and 15% (95% CI 6–28) in the dose-escalation phase (El-Khoueiry et al, 2017).

The safety and efficacy of pembrolizumab was evaluated in KEYNOTE-224. This phase 2, randomized, multicentre, open-label trial of pembrolizumab enrolled adults (≥ 18 years) with histologically confirmed advanced HCC with or without hepatitis C or B virus (HCV or HBV) infection. Previous sorafenib treatment was allowed. In this study, 104 eligible patients were treated. Pembrolizumab had a manageable safety profile that was generally similar to that of pembrolizumab in other tumour types. The ORR was 17% (95% CI 11–26). Among the 18 responders, the best overall responses were 1% complete response, 16% partial responses, 44% of participants had stable disease, 33% had progressive disease, and 6% could not be assessed because they did not have assessment data after baseline (Zhu et al, 2018).

As this is the first use of intrahepatic injection of talimogene laherparepvec with systemic IV administration of pembrolizumab, it is necessary to evaluate the safety of intrahepatic injection of talimogene laherparepvec in combination with systemic IV administration of pembrolizumab. As such, this study will evaluate potential blood and tumor biomarkers which predict and/or are correlated with clinical outcomes to intrahepatic injection of talimogene laherparepvec into liver tumors alone and in combination with intrahepatic injection of talimogene laherparepvec and systemic IV administration of pembrolizumab.

2.6 Clinical Hypotheses

PART 1:

Monotherapy cohorts 1-4: Talimogene laherparepvec injected intrahepatically into liver tumors will be safe in subjects with non-HCC with liver metastases and subjects with HCC without active viral hepatitis as assessed by subject incidence of DLTs.

Combination cohorts 5 and 6: Talimogene laherparepvec injected intrahepatically into liver tumors in combination with systemically administered pembrolizumab will be safe in subjects with non-HCC with liver metastases and subjects with HCC with and without viral hepatitis as assessed by subject incidence of DLTs.

PART 2:

Talimogene laherparepvec injected intratumorally in combination with systemic IV administration of pembrolizumab will demonstrate at least a 40% ORR in each tumor

type and be safe in the individual non-HCC tumor types as well as primary HCC with and without viral hepatitis.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a phase 1b/2, multicenter, open-label, basket trial to evaluate the safety of talimogene laherparepvec injected intrahepatically into liver tumors alone and in combination with systemic IV administration of pembrolizumab, in subjects with non-HCC liver metastases from BC, CRC, GEC, melanoma, NSCLC, RCC in Part 1 Group A, and subjects with HCC with and without viral hepatitis in Part 1 Group B (viral hepatitis is only applicable in combination setting), and to evaluate the efficacy and safety of intratumoral talimogene laherparepvec in combination with systemic pembrolizumab to treat subjects with advanced TNBC, hormone receptor positive breast cancer, CRC, CSCC, and BCC in Part 2 Group A and subjects with HCC with and without viral hepatitis in Part 2 Group B. **NOTE: as of Protocol Amendment 6 [dated 26 October 2021], intrahepatic injections of talimogene laherparepvec and liver biopsies are no longer performed in this study.** The study consists of 2 parts and 2 groups and Part 2 includes 2 stages.

The overall study design is described by a Study Design and Treatment Schema at the end of the protocol synopsis section.

The study endpoints are defined in Section 10.1.1.

3.1.1 Study Design for Part 1

Part 1 is a dose escalation study to evaluate the safety of intrahepatic injection of talimogene laherparepvec into liver tumors alone and in combination with systemic IV administration of pembrolizumab, and will consist of 2 groups: Group A (non-HCC) and Group B (HCC) (with and without viral hepatitis; viral hepatitis is only applicable in combination setting). The starting dose concentration used for this study will be at 10^6 PFU/mL for the first cycle (to convert HSV-seronegative subjects to seropositive and reduce the possibility of intolerance in these subjects) followed by 10^7 PFU/mL with volumes initially up to 4 mL with 21 days separating doses, which is consistent with the highest dose administered in the 005/04 pancreatic tumor injection study (Chang et al, 2012). Progression of the study through dosing cohorts in Part 1 and selections of MTC (see Table 1 and Study Design and Treatment Schema) and MTV will depend on the DLT evaluations that occur for each cohort. For talimogene laherparepvec monotherapy, safety will be assessed for the non-HCC and HCC groups

based on the "3 + 3" design. The concentration of the first dose of talimogene laherparepvec in all cohorts will always be 10^6 PFU/mL. Maximum total volumes (up to 4 mL or 8 mL) and subsequent concentrations (10^7 or 10^8 PFU/mL) to be administered will depend on the specific cohort (refer to Table 1). Combination cohorts (Cohorts 5 and 6) in Part 1 will determine the safety of administering intrahepatic injection of talimogene laherparepvec in combination with systemic IV administration of pembrolizumab using a modified toxicity probability interval (mTPI) up-and-down design.

Table 1. Part 1 Cohort Dependencies

MONOTHERAPY COHORTS		
	DLT ≥ 1/3 in 6 subjects	**DLT < 1/3 in 3 to 6 subjects**
Group A Cohort 1	Hold study in treatment group	Open Group A Cohort 2 Open Group B Cohort 1
Non-HCC (Group A) or HCC (Group B)[a]		
Cohort 1 (4 mL of 10^7 PFU/mL T-VEC)	Hold study in treatment group	Open Group B Cohort 2[b] Open Cohort 5 in corresponding group
Cohort 2[c] (4 mL of 10^8 PFU/mL T-VEC)	Open Cohort 4 • Set MTC to 10^7 PFU/mL in monotherapy	Open Cohort 3 • Set MTC to 10^8 PFU/mL in monotherapy
Cohort 3[d] (8 mL of 10^8 PFU/mL T-VEC)	Open Cohort 4, if: Part 2 dose for talimogene laherparepvec not determined yet OR Part 2 concentration for talimogene laherparepvec is determined to be 10^7 PFU/mL	• Use maximum tolerated volume of 8 mL talimogene laherparepvec in Part 2
Cohort 4[e] (if needed) (8 mL of 10^7 PFU/mL T-VEC)	Retain maximum volume of 4 mL talimogene laherparepvec in Part 2	Introduce volumes up to 8 mL talimogene laherparepvec in Part 2
COMBINATION COHORTS		
Non-HCC (Group A) or HCC with and without viral hepatitis (Group B)	**Initial or Subsequent mTPI Outcome[f]**	
Cohort 5 (4 mL of 10^7 PFU/mL T-VEC + pembrolizumab	D or DU: Stop; Hold study in treatment group S: Stay; expand cohort	E: Escalate to Cohort 6 if sample size is allowed and no DU from the previous decision.
Cohort 6 (Group A only)	DU: De-escalate to Cohort 5 and do not re-escalate D: De-escalate to Cohort 5	S or E: DLRT can declare MTC as 10^8 PFU/mL, or expand Cohort 6
Cohort 6a[g] (4 mL of 10^8 PFU/mL T-VEC + pembrolizumab	DU: De-escalate to Cohort 5 and do not re-escalate D: De-escalate to Cohort 5	S or E: DLRT can declare MTC as 10^8 PFU/mL, or expand Cohort 6a If S or E after at least 4 DLT evaluable subjects: open Cohort 6b

Footnotes on the next page

Table 1. Part 1 Cohort Dependencies

COMBINATION COHORTS		
Cohort 6b[g] (well-controlled viral hepatatis) (4 mL of 10^8 PFU/mL T-VEC + pembrolizumab	D or DU: Stop; No further exploration of this cohort.	S or E: DLRT can declare MTC as 10^8 PFU/mL for both Cohort 6a and 6b

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D = de-escalate to the next lower dose; DLRT = Dose Level Review Team; DLT = dose limiting toxicity; DU = de-escalate to the next lower dose/the current dose is unacceptably toxic; E = escalate; HCC = hepatocellular carcinoma; MTC = maximum tolerated concentration; mTPI = modified toxicity probability interval; PFU = plaque forming unit; S = stay at current dose; T-VEC = talimogene laherparepvec.

[a] Prior to Institutional Review Board (IRB) approval of Amendment 2, the opening of Group A Cohort 2 and Group B Cohort 1 was dependent on Group A Cohort 1 results. After IRB approval of Amendment 2, Group A and Group B are independent of each other.

[b] Group A Cohort 2 opened prior to IRB approval of Amendment 2.

[c] If Cohort 6 is deemed safe, then cohort 2 will stop enrolling in the respective Group.

[d] If Cohort 3 is deemed safe in either Group A or B, further enrollment into cohort 3 into either group will be suspended, then up to 8 mL will be used in Part 2 for Group A and B.

[e] Cohort 4 will be opened only if one of these conditions are met: 1) DLT rate ≥ 1/3 in Cohort 2; 2) DLT rate ≥ 1/3 in Cohort 3 and Part 2 dose for talimogene laherpare**p**vec not determined yet; or 3) DLT rate ≥ 1/3 in Cohort 3 and Part 2 concentration for talimogene laherparepvec is determined to be 10^7 PFU/mL.

[f] Refer to Section 3.1.4.2 and Table 17 for mTPI dose decision outcomes

[g] Group B only.

3.1.1.1 Part 1 Monotherapy Cohorts: Non-HCC Subjects (Group A) and HCC Without Viral Hepatitis Subjects (Group B)

Part 1 of the study will enroll subjects with non-HCC (BC, CRC, GEC, melanoma, NSCLC, or RCC) with liver metastases (Group A) and HCC subjects without viral hepatitis (Group B). Both Group A and B will each consist of at most 4 sequential monotherapy dose cohorts.

Cohort 1 will enroll from 3 to 6 DLT-evaluable subjects administering a maximum of 4 mL talimogene laherparepvec. Subjects in Cohort 1 will be administered 10^6 PFU/mL of talimogene laherparepvec in the first cycle. Twenty-one (+3) days later they will be administered 10^7 PFU/mL of talimogene laherparepvec to start the second cycle. Subsequent cycles (1 dose per cycle) will be given every 21 days (Q21D) (± 3 days), for a total of 6 cycles with an optional 6 additional cycles (see Section 3.1.3).

Cohort 2 will enroll from 3 to 6 DLT-evaluable subjects administering a maximum of 4 mL talimogene laherparepvec. Subjects in Cohort 2 will be administered 10^6 PFU/mL of talimogene laherparepvec for the first cycle. Twenty-one (21) (+ 3) days later they will be administered 10^8 PFU/mL of talimogene laherparepvec to start the second cycle. Subsequent cycles (1 dose per cycle) will be given every 21 days (Q21D) (± 3 days), for a total of 6 cycles with an optional 6 additional cycles (see Section 3.1.3).

Cohort 3 will enroll from 3 to 6 DLT-evaluable subjects administering a maximum of 8 mL talimogene laherparepvec. Subjects in Cohort 3 will be administered 10^6 PFU/mL of talimogene laherparepvec for the first cycle, and 10^8 PFU/mL of talimogene laherparepvec, up to 8 mL, 21 days later (+ 3 days) and Q21D (± 3 days) for a total of 6 cycles, with an optional 6 additional cycles (see Section 3.1.3).

Cohort 4 will be opened only if any of the following scenarios occur: 1) DLT rate ≥ 1/3 in Cohort 2; 2) DLT rate ≥ 1/3 in Cohort 3 and Part 2 dose for talimogene laherpare**p**vec not determined yet; or 3) DLT rate ≥ 1/3 in Cohort 3 and Part 2 concentration for talimogene laherparepvec is determined to be 10^7 PFU/mL. Subjects in this cohort will be administered a maximum of 8 mL talimogene laherparepvec. Subjects will be administered 10^6 PFU/mL of talimogene laherparepvec for the first cycle, and 10^7 PFU/mL of talimogene laherparepvec, up to 8 mL, 21 days later (+ 3 days) and Q21D (± 3 days) for a total of 6 cycles, with an optional 6 additional cycles (see Section 3.1.3).

If both Cohorts 3 or 4 and the combination cohorts (5 or 6) are open in the same institution, subjects with a tumor burden who can receive 8 mL (see Section 6.2.1.1) enrollment into Cohorts 3 or 4 must be strongly preferred until the MTV in monotherapy is determined.

Refer to Table 1 and the Study Design and Treatment Schema at the end of the synopsis section for additional information regarding progression of the study through the monotherapy dosing cohorts in Part 1.

3.1.1.2 Part 1 Combination Cohorts: Non-HCC Subjects (Group A) and HCC Subjects With and Without Viral Hepatitis (Group B)

Safety of the combination will be evaluated with the mTPI up-and-down design in Part 1 to determine the talimogene laherparepvec MTC with a target DLT rate of 40%. A maximum of 28 DLT-evaluable subjects will be enrolled across Cohort 5 and Cohort 6 in Group A and a maximum of 28 DLT evaluable subjects will be enrolled across Cohort 5 and Cohort 6a (without viral hepatitis) in Group B. A maximum of 12 DLT evaluable subjects will be enrolled in Cohort 6b (with viral hepatitis) in Group B. The MTC used as part of the recommended phase 2 dose (RP2D) will be selected as the highest cohort concentration with an mTPI outcome of either S (stay at the current dose) or E (escalate to the next higher dose) at the last Dose Level Review Team (DLRT) analysis. Full details of the mTPI design implementation will be specified in the DLRT Charter.

Cohort 5 will begin enrollment if and when safety is established from Cohort 1 in the respective non-HCC and HCC groups. Subjects in Cohort 5 will be administered a maximum total volume of 4 mL talimogene laherparepvec in combination with pembrolizumab. The minimum and maximum number of DLT-evaluable subjects for a dose decision will be specified in the DLRT Charter. Subjects in Cohort 5 will be administered a concentration of 10^6 PFU/mL for the first cycle and 10^7 PFU/mL for talimogene laherparepvec, up to 4 mL, 21 (+ 3) days later, and Q21D (± 3 days) for a total of 6 cycles, with an optional 6 additional cycles (see Section 3.1.3). Pembrolizumab at 200 mg Q3W can be administered for up to 35 cycles (approximately 24 months) (see Section 3.5.1 for additional study duration details).

If the mTPI outcome for Cohort 5 is E, then Cohort 6 (Group A) or Cohort 6a (Group B) will open. If cohort 6b completes sooner than 6a, and 6b is deemed safe, then cohorts 5 and 6a will stop enrollment, and both 6a and 6b are deemed safe. Subjects in Cohort 6 (Group A) or 6a (Group B) will be administered a concentration of 10^6 PFU/mL for the first cycle and 10^8 PFU/mL of talimogene laherparepvec, up to 4 mL, 21 (+ 3) days later, and Q21D (± 3 days) for a total of 6 cycles with an optional 6 additional cycles (see Section 3.1.3). Pembrolizumab at 200 mg Q3W can be administered for up to 35 cycles (approximately 24 months) (see Section 3.5.1 for additional study duration details).

If the mTPI outcome for Cohort 6a (without viral hepatitis) for Group B is S or E after a minimum of 4 DLT evaluable subjects, then Cohort 6b (with viral hepatitis) in Group B will open. Subjects in Cohort 6b will be administered a concentration of 10^6 PFU/mL for the first cycle and 10^8 PFU/mL of talimogene laherparepvec, up to 4 mL, 21 (+ 3) days later, and Q21D (± 3 days) for a total of 6 cycles with an optional 6 additional cycles (see Section 3.1.3). Pembrolizumab at 200 mg Q3W can be administered for up to 35 cycles (approximately 24 months) (see Section 3.5.1 for additional study duration details).

Due to the mTPI up-and-down design, there is the possibility of de-escalating and re-escalating between Cohort 5 and 6. There will be no de-escalation for Cohort 6b (Group B) if the mTPI outcome is D or DU, and Cohort 6b will close if D or DU is obtained. Please see Table 1 above for more details.

3.1.2 Study Design for Part 2 (Non-HCC and HCC Groups)

Part 2 is a 2-stage design to evaluate the efficacy of talimogene laherparepvec in combination with systemic pembrolizumab separately by tumor type. The DLRT will consider prospective guidelines in the DLRT Charter to monitor safety in Part 2

separately by tumor type and, if introduced, talimogene laherparepvec total volumes $>$ 4 mL within Group A and Group B as discussed in Section 10. Subjects will be enrolled into one of the following treatment groups and arms based on the underlying tumor type:

- Group A (non-HCC):
  - Arm I: Hormone receptor positive breast cancer
  - Arm II: TNBC
  - Arm III: CSCC
  - Arm IV: BCC
  - Arm V: CRC
- Group B (HCC):
  - Arm VI: HCC with or without viral hepatitis

Part 2 (Group A) of the study will enroll subjects of non-HCC tumors (hormone receptor positive BC, TNBC, CSCC, CRC, BCC). Subjects will be enrolled separately into each tumor type. Stage 1 of Part 2 (Group A) will begin enrolling after MTC has been determined from Cohort 5 and 6 in Part 1.

Part 2 (Group B) of the study will enroll subjects with HCC with and without viral hepatitis. Stage 1 of Part 2 (Group B) will begin enrolling after MTC has been determined from Cohorts 5 and 6 in Part 1.

Subject enrollment and study conduct during Part 2 of the study will progress independently in the non-HCC and HCC groups.

During Stage 1 of Part 2, non-HCC and HCC groups will enroll approximately 10 subjects for each tumor type arm (5 tumor type arms in Group A and 1 tumor type arms in Group B with and without viral hepatitis). Subjects with specific tumor types from the combination cohorts in Part 1 (Cohorts 5 and 6) that are treated at the MTC used in Part 2, will not be included as part of the enrollment numbers for that tumor type arm in Part 2. Subjects enrolled in Part 2 will initially be administered up to 8 mL of talimogene laherparepvec MTC determined from Cohorts 5 or 6 in Part 1. Administration of up to 8 mL of talimogene laherparepvec was established from Part 1, Cohort 3 of either Group, any newly enrolled subjects in Part 2 can be administered up to 8 mL of talimogene laherparepvec. No intrasubject concentration or volume

escalation is allowed. The primary analysis of efficacy will include subjects that receive any volume of talimogene laherparepvec (monotherapy cohorts) and subjects that receive any volume of talimogene laherparepvec and pembrolizumab (combination cohorts). Stage 1 of a 2-stage efficacy assessment will occur once 10 subjects have been enrolled in a tumor type arm. Stage 1 efficacy assessments will occur separately per tumor type arm. If efficacy is not futile, Stage 2 will open for that particular tumor type arm where approximately an additional 11 subjects can be enrolled.

3.1.3 Optional Additional Dosing for Talimogene Laherparepvec

After the subjects in either Part 1 or Part 2 have received the first 6 cycles of talimogene laherparepvec, there is an option to continue dosing with up to 6 additional cycles (Part 1 only) or a maximum of 35 cycles (Part 2) of talimogene laherparepvec at the same dose level as in cycles 2 to 6 provided that the subject has lesions to inject, has not reached a confirmed progressive disease (PD) by modified immune-related response criteria (irRC) simulating RECIST version 1.1 (irRC-RECIST; Nishino et al, 2014), has not had rapid clinical deterioration or worsening symptomatic disease, has not had intolerance of treatment, has no significantly better alternative treatment options in the opinion of the investigator, and agrees to the additional doses of talimogene laherparepvec after investigator discussion with the medical monitor (medical monitor approval required in Part 1 only). In Part 2, additional dosing of talimogene laherparepvec beyond a total of 12 cycles of talimogene laherparepvec may be allowed if in the opinion of the investigator and after discussion with the medical monitor, the subject is deriving clinical benefit from the study regimen, the subject is still receiving pembrolizumab.

3.1.4 Safety Evaluation for Parts 1 and 2

A DLRT, consisting of an Amgen medical clinician, safety representative, biostatistician, Global Clinical Study Manager (GCTM), representative(s) from Merck, and at least one participating investigator who enrolled subjects into Part 1 and/or Part 2, will review the safety data to evaluate the subject incidence of DLTs and adverse events. Representative(s) from Merck will participate in DLRT meetings for all cohorts (voting member only for cohort 5 and 6 of Part 1 and all cohorts in Part 2). The DLRT will make recommendations in Part 1 according to the DLT 3 + 3 rules for monotherapy cohorts, mTPI up-and-down design rules for combination cohorts, and in Part 2 the DLRT will make recommendations considering prospective guidelines to monitor safety, in the DLRT Charter. For each dosing cohort in Part 1, the DLRT will recommend either to enroll more subjects for DLT evaluation, to prematurely stop enrollment, or to declare the

dose tolerable. In Part 2, the DLRT may consider reducing the RP2D talimogene laherparepvec concentration and/or discontinuation of total volumes > 4 mL, if introduced. If the concentration is reduced in Part 2 for a tumor type arm, then the sample size considerations for the 2-stage futility and efficacy analyses of that tumor type arm will include only subjects treated at the reduced concentration. The DLRT can consider the totality of available clinical data when reviewing a given cohort.

3.1.4.1 Rules for DLT Evaluation and Dose Escalation for Part 1

Monotherapy Cohorts:

The DLT evaluation period for a given subject will consist of the period between the initial 10^6 PFU/mL dose of talimogene laherparepvec and 3 weeks following the initial 10^7 or 10^8 PFU/mL dose of talimogene laherparepvec. A subject will be considered to have had a DLT if they experience a DLT event (as outlined in Section 3.1.4.3) during the DLT evaluation period. Any subject who discontinues treatment or is lost to follow-up before the end of the DLT evaluation period for any reason other than DLT will not be considered evaluable for DLT and may need to be replaced by another subject in the same cohort.

Combination Cohorts:

The DLT evaluation period for a given subject will consist of the period between the initial 10^6 PFU/mL concentration of talimogene laherparepvec and 3 weeks following the initial 10^7 or 10^8 PFU/mL dose of talimogene laherparepvec. Any subject who has not received at least 2 doses of talimogene laherparepvec (10^6, and 10^7 or 10^8 PFU/mL) and 2 doses of pembrolizumab, will not be considered DLT-evaluable unless they experience a DLT after the first dose. A subject will be considered to have had a DLT if they experience a DLT event (as outlined in Section 3.1.4.3) during the DLT evaluation period. Any subject who discontinues treatment, or is lost to follow-up before the end of the DLT evaluation period for any reason other than DLT, will not be considered evaluable for DLT and may need to be replaced by another subject in the same cohort.

The DLRT will meet whenever 3 to 6 subjects in each monotherapy dose cohort (Cohorts 1, 2, 3, and 4) of Part 1 or when a sufficient number of additional subjects (per the DLRT Charter), in the combination treatment cohorts (Cohorts 5 and 6 [including 6a and 6b]) in Part 1 are evaluable for subject incidence of DLT, and a decision regarding cohort escalation/modification is being considered. The DLRT will declare a dose safe for Cohorts 1, 2, 3, and 4 if the subject incidence of DLT is < 1/3 during the DLT evaluation period subject to the following rules:

Monotherapy Cohorts (Cohorts 1, 2, 3, and 4) of Part 1. See Section 3.1.4.2 below for combination therapy (Cohorts 5 and 6):

- If no subjects among the initial 3 evaluable subjects in Part 1 experience DLT, then the dose will be deemed safe.
- If 1 subject among the initial 3 evaluable subjects in Part 1 experiences DLT, an additional 3 evaluable subjects will be enrolled.
- If < 2 subjects among the expanded cohort of 6 evaluable subjects in Part 1 experience DLT, then the dose will be deemed safe.
- If ≥ 2 subjects among the initial 3 evaluable subjects or among the expanded cohort of 6 evaluable subjects experiences a DLT, then the dose will be declared not safe.

Additional DLRT meetings will occur after additional DLT-evaluable subjects in each dose cohort of Part 1 of Group A and Group B, respectively, are enrolled per above DLT rules. The MTC will be determined as the highest concentration (either 10^7 or 10^8 PFU/mL) evaluated with a subject incidence of DLT $< 1/3$ between Cohorts 1 and 2, and the MTV will be determined as the highest volume (4 or 8 mL) evaluated with a subject incidence of DLT $< 1/3$ between Cohorts 1, 2, 3, and 4. The MTC for Part 2 is established from Cohorts 5 and 6. If the initial MTV in Part 2 is 4 mL, the MTV for Part 2 will change to 8 mL, if and when, safety of administering the higher volume is established from Cohorts 3 and 4 in Part 1.

3.1.4.2 Safety Evaluation for Combination Therapy in Parts 1 and 2

For subjects enrolled in combination therapy (Cohort 5 and 6) in Part 1, safety will be evaluated separately for each Group (A and B) with a common mTPI up-and-down design to determine the talimogene laherparepvec MTC for each Group with a target DLT rate of 40%. For Cohorts 5 and 6 in Part 1, the mTPI model will be used for each Group (A and B). A review of safety data in Part 1 will occur when a sufficient number of additional DLT-evaluable subjects (per the DLRT Charter), have been enrolled in a Group.

For Part 2, the DLRT will consider prospective guidelines in the DLRT Charter to monitor safety within Group A and Group B and, if introduced, talimogene laherparepvec total volumes > 4 mL within Group A and Group B. During Part 2 of the study, a planned review of efficacy data will occur after a total of 10 treated subjects have been enrolled in a particular tumor type arm with at least 20 weeks minimum potential follow-up (see Section 10.2 and Section 10.3.1.2 for more details). An interim safety data review will occur for each tumor type separately after approximately 10 subjects have been treated in Part 2 with the specific tumor type with at least 6 weeks of follow-up.

The enrollment will be suspended after 10 treated subjects for a particular tumor type for the Stage 1 efficacy futility analysis if a non-futile efficacy outcome cannot be verified after the 10th treated subject. The subject incidence of DLT and adverse events will be monitored in Part 2 and additional safety analyses may be conducted as warranted during the conduct of the study at the discretion of the DLRT.

3.1.4.3 Definition of DLT

All toxicities will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (Appendix A).

The occurrence of any of the following toxicities during DLT evaluation period (ie, occurred during the first 2 dosing cycles) will be considered a DLT, if judged by the investigator to be related to talimogene laherparepvec and/or pembrolizumab:

- Grade 4 non-hematologic toxicity
- Grade 3 non-hematologic toxicity lasting > 3 days despite optimal supportive care, except grade 3 fatigue
- Any grade 3 or higher non-hematologic laboratory value if medical intervention is required, leads to hospitalization, or persists for > 1 week. Laboratory values that persist for > 1 week but are deemed not clinically important per both investigator and sponsor will not be considered DLTs
- Either AST or ALT 3x above baseline/upper limit of normal (ULN) (whichever is higher) AND either international normalization ratio (INR) or total bilirubin (TBL) 2x above baseline/ULN (whichever is higher)
- Grade 3 or 4 febrile neutropenia
  - Grade 3 is defined as absolute neutrophil count (ANC) < 1.0 x 10^9/L with a single temperature of > 38.3ºC (101ºF) 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 > 38.3ºC (101ºF) or sustained temperature of ≥ 38ºC (100.4ºF) for more than 1 hour, with life-threatening consequences and urgent intervention indicated
- Grade 4 thrombocytopenia associated with a bleeding event requiring intervention
  - 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
- Serious herpetic event: Herpetic encephalitis, encephalomyelitis, or disseminated herpetic infection
- Grade 5 toxicity (ie, death)
- Any other intolerable toxicity leading to permanent discontinuation of talimogene laherparepvec and/or pembrolizumab

- Grade 3 or higher adverse events related to talimogene laherparepvec and/or pembrolizumab, that results in a study treatment delay by > 2 weeks

If a subject experiences a DLT during the DLT evaluation period, study treatments will be discontinued for that subject. However, if a subject demonstrates clinical benefit as assessed by the treating physician, the investigator or designee should notify the sponsor's medical monitor as soon as possible. Subjects may be allowed to remain on study treatment after discussion between the sponsor's medical monitor and the investigator to determine the appropriateness of treatment resumption. Prior to continuing study treatment, investigator will be required to document that, in the investigator's opinion, the subject continues to receive clinical benefit and that the subject agreed to continue following a discussion of all available treatment options.

3.2 Number of Sites

Approximately 50 sites located in the United States of America (USA), Europe, Australia, and Asia will participate in the study. Additional sites, countries, and regions may be added to the study as necessary. Sites that do not enroll subjects within 6 months of site initiation may be closed.

3.3 Number of Subjects

Participants in this clinical investigation shall be referred to as "subjects". **A total of 127** subjects **are enrolled in this study (74** subjects in Part 1; **53** subjects in Part 2).

Refer to Section 10.2 for sample size considerations.

3.4 Replacement of Subjects

Subjects enrolled and treated may be replaced in Part 1 if they are not evaluable for DLT (eg, did not receive talimogene laherparepvec or ended study treatment before completion of DLT-evaluation period for a reason other than experiencing a DLT). Dose-limiting toxicity non-evaluable subjects will not be replaced in Part 2. The minimum and maximum number of DLT-evaluable subjects for a dose decision will be specified in the DLRT Charter.

3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

The subject accrual period is planned to be approximately 58 months.

The estimated average per-subject study duration is approximately 32 months. The duration of the screening period for each subject will be up to 28 days. The duration of treatment will vary for each subject. Subjects can receive a maximum of 12 cycles of

talimogene laherparepvec in Part 1 and 35 cycles in Part 2. Subjects will be treated with talimogene laherparepvec until a CR is achieved, all injectable tumors have disappeared, PD per the modified irRC-RECIST (Appendix D), confirmed by 2 consecutive scans > 4 weeks apart (Nishino et al, 2014), intolerance of study treatment, a total of 6 cycles (including the initial 10^6 PFU/mL cycle) have been administered and in the investigator's opinion further talimogene laherparepvec is not advisable, the subject has received the maximum allowable cycles of talimogene laherparepvec, or the investigator determines it is in the best interest of the subject to discontinue treatment (eg, rapid clinical deterioration or worsening symptomatic disease requiring alternative systemic anti-cancer therapy), whichever occurs first. Confirmation of disease progression is required only in the absence of rapid clinical deterioration (ie, rapid decline in performance status or requiring other therapy) or worsening symptomatic disease requiring a rapid switch to alternative systemic anti-cancer therapy.

Subjects can receive up to 35 cycles (approximately 24 months) with pembrolizumab. During that time, subjects may continue until PD per the modified irRC-RECIST (Appendix D), unacceptable toxicity, withdrawal of consent, physician's decision to stop therapy for the subject, or sponsor's decision to terminate the study. Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 8 cycles (24 weeks) with pembrolizumab, and had at least 2 cycles of pembrolizumab beyond the date when the initial CR was declared.

Subjects will be followed for safety for approximately 30 (+ 7) days after the last dose of talimogene laherparepvec for the monotherapy cohorts, and after the last dose of talimogene laherparepvec or pembrolizumab, whichever is later, for the combination treatment (Cohort 5 and 6 in Part 1, and all arms in Part 2).

For Part 1, contact for all subjects will be attempted approximately every 12 weeks (± 28 days) following the safety follow-up visit until death, subject withdrawal, or up to approximately 24 months after the date of the last subject enrolled in Part 1. Subjects in Cohort 5 and 6 will be followed approximately 24 months after the last subject enrolled in their cohort in Part 1, or approximately 24 months after the last subject enrolled with their tumor type in Part 2, whichever is later.

For Part 2, contact for all subjects will be attempted approximately every 12 weeks (± 28 days) following the safety follow-up visit until death, subject withdrawal, or up to approximately 24 months after the date of the last subject enrolled in that tumor cohort.

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 endpoints, whether the study concluded as planned in the protocol or was terminated early. The primary completion date is the date when all subjects (Parts 1 and 2) have a minimum potential follow-up of ≥ 29 weeks.

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 Trial: The end of study date is defined as the date when the last subject 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. The end of study will occur when the last subject discontinues talimogene laherparepvec and/or pembrolizumab (whichever is later) and has had the opportunity to complete both the safety follow-up visit and the long-term survival follow-up (which is up to approximately 24 months after the date of the last subject enrolled in Part 2).

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, tumor type). Screening logs may be required to be shared with Amgen.

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

As of Protocol Amendment 6 (dated 26 October 2021), intrahepatic injections of talimogene laherparepvec and liver biopsies are no longer performed in this study. Enrollment for this study has stopped.

4.1 Inclusion and Exclusion Criteria

4.1.1 Inclusion Criteria

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

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

114 Subjects must have histologically or cytologically confirmed disease.

- Part 1 is restricted to BC, CRC, GEC, melanoma, NSCLC, or RCC with liver metastasis or HCC.

- Part 2 Group A is restricted to advanced hormone receptor positive BC, TNBC, CSCC, CRC and BCC with or without liver metastases.
    - Part 2 Hormone receptor positive Breast Cancer Arm only: Histologically and/or cytologically confirmed diagnosis of ER positive and/or PrR positive (ER ≥ 1%, PrR ≥ 1%) breast cancer.
    - Triple negative breast cancer: Histologically and/or cytologically confirmed diagnosis of ER negative, PrR negative, human epidermal growth factor receptor 2 (HER2)-Neu negative (ER < 1%; PrR < 1%; HER2-Neu < 3+ by immunohistochemistry or fluorescence in situ hybridization ratio ≤ 2.2 or < 6 copies HER2 gene copies/nucleus) (Wolff et al, 2007; Hammond et al, 2010). Subjects with unresectable locally recurrent TNBC are eligible.
- Part 2 Group B is restricted to HCC (fibrolamellar and mixed hepatocellular/cholangiocarcinoma subtypes are not eligible).

112 HCC subjects with well-controlled viral hepatitis Cohort 6b: Subjects must have a diagnosis of hepatitis B and/or C (HBV and HCV).

116 HCC subjects with well-controlled viral hepatitis Cohort 6b and Arm VI: Subjects with HCV infection must have completed treatment for their hepatitis C at least 4 weeks prior to study enrollment, and HCV viral load must be undetectable.

Subjects with controlled HBV will be eligible as long as they meet the following criteria:

- Antiviral therapy for HBV must be given for at least 4 weeks and HBV viral load must be < 100 IU/mL prior to enrollment. Participants on active HBV therapy with viral loads < 100 IU/mL should stay on the same therapy throughout study treatment.
- Subjects who are positive for anti-hepatitis B core antibody HBc, negative for hepatitis B surface antigen (HBsAg), and negative or positive for anti-hepatitis B surface antibody (HBs), and who have an HBV viral load < 100 IU/mL, do not require HBV anti-viral prophylaxis.

104 Non-HCC subjects with progression on or following at least 1 prior standard of care systemic anti-cancer therapy (eg, chemotherapy, hormone therapy, targeted therapy) for locally advanced or metastatic disease. For the combination cohorts (Cohorts 5 and 6 in Part 1) and Part 2, subjects with melanoma NSCLC or CSCC do not need to have received prior therapy. Subjects with HCC do not necessarily need to be treated previously with prior systemic anti-cancer therapy. If no standard of care therapies exist for the subject, or the subject cannot tolerate or refuses standard of care anti-cancer therapy, the subject may be allowed to participate on the study after discussion between the investigator and Amgen medical monitor.

113 Subjects with measurable disease.

- In Part 1, measurable disease as defined by:

  at least 1 liver lesion that can be accurately and serially measured in at least 1 dimension and for which the longest diameter is ≥ 10 mm (non-HCC) or

≥ 20 mm (HCC) as measured by multiphase CT scan or magnetic resonance imaging (MRI)

lesion(s) must not be from an area of the liver that received prior localized therapies (eg, radiation, ablation, embolization), unless there is documented evidence of disease progression in the area that is measurable and distinguishable from the effects of prior therapy prior to enrollment

- In Part 2, at least 1 measurable lesion by CT scan or MRI as defined by RECIST 1.1 (Eisenhauer et al, 2009).

115 All Part 1 subjects and any Part 2 subjects where liver injection is planned:

at least one injectable liver lesion without necrosis ≥ 10 mm in longest diameter or at least one liver lesion with necrosis where the longest diameter of the necrotic region subtracted from longest diameter of the lesion is ≥ 10 mm

tumors selected for injection must not be located where any potential tumor swelling after injection may lead to significant biliary tract obstruction (eg, < 1 cm adjacent to the left main, right main, or common biliary ducts) or where there may be significant risk of bleeding (eg, < 1 cm from the hepatic capsule)

Part 2 only:

Subjects where deep lymph node injections are planned:

Lesions selected for injection must not, in the investigator's opinion, be located where any potential tumor swelling after injection may lead to significant morbidity or obstruction or where there may be significant risk of bleeding

107 Cohort 3 and 4: sum of tumor diameters from injectable lesions is at least 8 cm (or possibly greater if there are lesions with necrotic cores) and must be eligible to receive> 4 mL of talimogene laherparepvec as defined in Section 6.2.1.1

108 Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (see Appendix G)

109 Life expectancy approximately 5 months or more

110 Adequate organ function determined within 10 days prior to enrollment, defined as follows:

- Hematological (without need for transfusion and or growth factor support within 10 days):
  - ANC ≥ 1500/mm^3 (1.5 x 10^9/L)
  - platelet count ≥ 100 000/mm^3 (100 x 10^9/L)
  - hemoglobin ≥ 9 g/dL (90 g/L)
- Renal:
  - serum creatinine ≤ 1.5 x 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 TBL ≤ 1.5 x ULN
  - AST ≤ 5 x ULN
  - ALT ≤ 5 x ULN
  - Alkaline phosphatase (ALP) ≤ 5 x ULN
- Coagulation:
  - Prothrombin time (PT) or INR ≤ 1.5 x ULN partial thromboplastin time (PTT) or activated PTT (aPTT) ≤ 1.5 x ULN

111 Child-Pugh score of A (Appendix F)

4.1.2 Exclusion Criteria

Exclusion for all subjects (monotherapy and combination subjects):

201 Candidate for any surgery or locoregional therapy for their cancer with curative intent.

202 More than one-third of the liver estimated to be involved with tumor

203 Candidate for whom systemic anti-cancer therapy is planned in the immediate future, with the exception of immunotherapy in the combination cohorts (Cohorts 5 and 6 in Part 1 and all subjects in Part 2).

235 All Part 1 subjects and any subject planned to have intrahepatic injections during the first cycle:

- Currently receiving, or less than 28 days prior to enrollment since receiving liver tumor-directed therapy (eg, radiation, ablation, embolization),

All Subjects:

- Currently receiving, or less than 28 days prior to enrollment since receiving antibody-based therapy, or immunotherapy or hepatic surgery or major surgery; or less than 28 days prior to enrollment since receiving radiation therapy to a site of planned injection for the first cycle, or less than 21 days prior to enrollment since receiving chemotherapy; or less than 14 days prior to enrollment from receiving targeted small molecule therapy or hormonal therapy.

236 Part 1:

- Any tumor type with history of central nervous system (CNS) metastases or carcinomatous meningitis.

Part 2:

- History or evidence of active CNS metastases, except subjects with previously treated 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

have not required steroids, for at least 1 month prior to enrollment. Carcinomatous meningitis is excluded regardless of clinical stability.

206 History of organ transplant.

207 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.

238 Has a history of (non-infectious) pneumonitis / interstitial lung disease that required steroids or has current pneumonitis / interstitial lung disease.

208 Evidence of clinically significant immunosuppression such as:

- primary immunodeficiency state such as Severe Combined Immunodeficiency Disease.
- concurrent opportunistic infection.
- requires concomitant treatment with immunosuppressive agents, including chronic oral or systemic steroid medication use at a dose of $>$ 10 mg/day of prednisone or equivalent or has received $>$ 10 mg/day of prednisone or equivalent within 7 days of enrollment. Subjects that require intermittent use of steroid inhalers, topical steroids, or local steroid injection will not be excluded from the study.

209 Non-HCC: has acute or chronic active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection.

210 Part 1 Group B cohort 1-5, 6a, and Part 2 Arms I-V:

- History of HBV and/or HCV infection with viral load detectable by real-time polymerase chain reaction (qPCR) testing (with sensitivity to detect at least a minimum of 20 IU/mL); or received treatment with nucleotide analogs such as those used in the treatment of HBV (eg, lamivudine, adefovir, tenofovir, telbivudine, entecavir), ribavirin, or interferon alpha within 12 weeks of initiation of study treatment for control of hepatitis B or C.

Part 1 Group B cohort 6b and Part 2 Arm VI :

- Subjects with concurrent well-controlled viral hepatitis B and hepatitis C, unless subject fulfills all the eligibility criteria for Hepatitis B and hepatitis C stated in eligibility criteria 116.

211 All Part 1 subjects and any subject planned to have intrahepatic injections:

Has macroscopic intravascular invasion into the main portal vein, hepatic vein, or vena cava.

212 Known to have human immunodeficiency virus (HIV) infection.

213 Active herpetic skin lesions or prior complications of HSV-1 infection (eg, herpetic keratitis or encephalitis).

214 Requires intermittent or chronic systemic (IV or oral) treatment with an anti-herpetic drug (eg, acyclovir), other than intermittent topical use.

215 All Part 1 subjects who require concomitant treatment with warfarin. Other anticoagulants (ie, low molecular weight heparins, non-steroidal anti- inflammatory drugs) that do not prolong the PT/INR may be allowed after investigator discussion with the sponsor and as long as the institutional guidelines requiring their withholding for interventional radiology procedures can be followed.

All Part 2 subjects who receive an intrahepatic liver injection or liver biopsy and require concomitant treatment with warfarin. **As of Protocol Amendment 6 (dated 26 October 2021), intrahepatic injections of talimogene laherparepvec and liver biopsies are no longer performed in this study.** Other anticoagulants (ie, low molecular weight heparins, non-steroidal anti-inflammatory drugs) that do not prolong the PT/INR may be allowed as long as the institutional guidelines requiring their withholding for interventional radiology procedures can be followed.

216 Currently receiving treatment with another investigational device or drug study, or less than 28 days prior to enrollment since ending treatment with another investigational device or drug study(s).

217 Other investigational procedures while participating in this protocol are excluded.

218 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 for $\geq$ 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.
- adequately treated cervical carcinoma in situ without evidence of disease.
- adequately treated breast ductal carcinoma in situ without evidence of disease.
- prostatic intraepithelial neoplasia without evidence of prostate cancer.
- adequately treated urothelial papillary noninvasive carcinoma or carcinoma in situ.

219 Subject has known sensitivity to talimogene laherparepvec or its components to be administered during dosing.

220 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 28 days after the last dose of talimogene laherparepvec.

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

222 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 medical monitor, if consulted, would pose a risk to subject safety or interfere with the protocol evaluation, procedures or completion.

223 Subject has entered this protocol previously.

224 Female subject is pregnant or breast-feeding, or planning to become pregnant during protocol treatment and through 4 months after the last dose of talimogene laherparepvec or pembrolizumab, whichever is later. (Females of childbearing potential should only be included in the study after a negative highly sensitive urine or serum pregnancy test).

225 Female subjects of childbearing potential who are unwilling to use 1 acceptable method(s) of effective contraception during protocol treatment and through 4 months after the last dose of talimogene laherparepvec or pembrolizumab, whichever is later. Refer to Appendix H and Appendix I for additional contraceptive information.

226 Sexually active subjects and their partners who are unwilling to use a barrier method (eg, condom) to avoid potential viral transmission during sexual contact during and within 30 days after treatment with talimogene laherparepvec.

227 Has received a live-virus vaccination within 30 days of planned treatment start. Seasonal flu vaccines that do not contain live virus are permitted.

228 Prior therapy with talimogene laherparepvec or any other oncolytic viruses.

229 Prior therapy with tumor vaccine.

230 Has an active infection requiring systemic therapy.

231 Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

Additional Criteria for Combination treatment cohorts:

232 Toxic effect(s) of the most recent prior chemotherapy not resolved to Grade 1 or less (except alopecia). Unresolved toxicity and/or complications from received major surgery or radiation therapy of $>$ 30 Gy.

233 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 (ICF). Where required by local laws and regulations, additional country-specific contraception requirements may be defined in a country-specific protocol supplement at the end of the Appendix section of the protocol.

234 Has severe hypersensitivity (≥ Grade 3) to pembrolizumab and/or any of its excipients.

237 Part 2 Hormone receptor positive BC subjects who had prior treatment with a checkpoint inhibitor.

5. SUBJECT ENROLLMENT

Before subjects may be entered into the study, Amgen requires a copy of the site's written IRB/IEC approval of the protocol, ICF, and all other subject information and/or recruitment material, if applicable (see Section 11.2). All subjects must personally sign and date the ICF before commencement of study-specific activities /procedures (ie, non-standard of care procedures).

All subjects who enter into the screening period for the protocol (defined as the point when the subject signs the informed consent) must be registered as screened subjects in the interactive voice response (IVR) system and will receive a unique subject identification number before any protocol-specific procedures are performed. This number will be used to identify the subject throughout the study and must be used on all study documentation related to that subject. The subject identification number must remain constant throughout the entire study; it must not be changed at the time of rescreening or enrollment.

Subjects who are determined not eligible after screening must be screen-failed in the IVR system 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 re-consent to the study to ensure that the IRB/IEC-approved main ICF is signed within 28 days of enrollment. Subjects who are determined not eligible after rescreen must be screen-failed in the IVR system and the reason for the screen-failure provided. Subjects may be enrolled only once into this protocol.

Upon confirmation of eligibility, the site staff will use the IVR system to enroll a subject. A subject will be considered enrolled when the investigator confirms that the subject has met all eligibility criteria and the subject is registered as enrolled in the IVR system. The investigator is to document confirmation of eligibility in the subject's medical record and in the case report form (CRF).

5.1 Treatment Assignment

Treatment assignment will be managed through IVR system. Additional details on the process and method of assignments are available in the IVR system manual. The IVR system manual will be provided to each investigative site.

This is an open-label trial; therefore, Amgen, the investigator, and the subject will know the treatment administered. Subjects participating in this trial will be allocated by non-random assignment. Subjects will be enrolled according to their primary tumor type into Group A or Group B.

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

6. TREATMENT PROCEDURES

6.1 Classification of Product

The Amgen Investigational Product used in this study is talimogene laherparepvec.

The non-Amgen Investigational Product used in this study is 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 Product

6.2.1 Talimogene Laherparepvec

Talimogene laherparepvec will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures. Talimogene laherparepvec is supplied as a sterile frozen liquid in a single-use 2-cc Crystal Zenith (CZ resin) vial with a gray Fluorotec®-coated chlorobutyl elastomer stopper, aluminum seal, and polypropylene cap. Each vial contains a minimum of 1.0 mL talimogene laherparepvec at either 10^6 PFU/mL or 10^8 PFU/mL concentrations. The supply for 10^6 PFU/mL concentration will be packaged separately from the supply for 10^8 PFU/mL concentration. As necessary, talimogene laherparepvec 10^8 PFU/mL will be diluted 1:10 for a concentration of 10^7 PFU/mL immediately prior to injection.

6.2.1.1 Dosage, Administration, and Schedule

Talimogene laherparepvec 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 4.03 (Appendix A). Hematology, chemistry and coagulation panels should be obtained according to the Schedule of Assessments

(Table 8 through Table 13) and the results should be checked before each treatment administration. Dosing will occur only if these test values are acceptable, per Section 6.2.1.2.

In Part 1, talimogene laherparepvec will be administered by intralesional injection only into liver tumors, with US or CT guidance. In Part 2, talimogene laherparepvec will be administered by intralesional injection into liver tumors with US or CT guidance. In Part 2, intratumoral injection into lymph nodes, cutaneous or subcutaneous tumor lesions may be done with or without image guidance, based on investigator preference.

As of Protocol Amendment 6 (dated 26 October 2021), intrahepatic injections of talimogene laherparepvec and liver biopsies are no longer performed in this study.

PART 1:

The initial dose of talimogene laherparepvec is 10^6 PFU/mL up to 4 mL in Cohorts 1 and 2, and up to 8 mL in Cohorts 3 and 4 (if needed) of the non-HCC (Group A) and HCC (Group B) of Part 1. The subsequent concentrations and volumes used in the various cohorts are shown below in the table:

Table 2. Part 1 Dose Details for Each Cohort

Cohorts in Part 1	Talimogene laherparepvec Volume (mL)	Initial Talimogene Laherparepvec Concentration (PFU/mL)	Second and Subsequent Talimogene Laherparepvec Concentration (PFU/mL)	Pembrolizumab dose (mg)
1	4	10^6	10^7	n/a
2[a]	4	10^6	10^8	n/a
3[b]	8	10^6	10^8	n/a
4[c]	8	10^6	10^7	n/a
5	4	10^6	10^7	200
6[d]	4	10^6	10^8	200

DLT = dose limiting toxicity; PFU = plaque forming unit
[a] If Cohort 6 is deemed safe, then cohort 2 will stop enrolling in the respective Group
[b] If Cohort is deemed safe in either Group A or B, further enrollment into cohort 3 into either group will be suspended, then up to 8 ml will be used in Part 2 for Groups A and B.
[c] Cohort will be opened only if one of these conditions are met: 1) DLT rate ≥ 1/3 in Cohort 2;
2) DLT rate ≥ 1/3 in Cohort 3 and Part 2 dose for talimogene laherpare**p**vec not determined yet; or
3) DLT rate ≥ 1/3 in Cohort 3 and Part 2 concentration for talimogene laherparepvec is determined to be 10^7 PFU/mL
[d] Includes Group B Cohort 6a and Cohort 6b

The first cycle of talimogene laherparepvec will be 21 (+3) days (from the first dose at 10^6 PFU/mL to the second dose at 10^7 or 10^8 PFU/mL). Subsequent cycles of talimogene laherparepvec will be 21 (±3) days.

The maximum volume of talimogene laherparepvec administered at any dose is 4 mL (Cohorts 1, 2, 5, and 6) or 8 mL (Cohorts 3 and 4) for any individual lesion or for all lesions combined.

Part 2:

As of Protocol Amendment 6 (dated 26 October 2021), intrahepatic injections of talimogene laherparepvec and liver biopsies are no longer performed in this study.

In Part 2, talimogene laherparepvec can be administered into liver lesions, lymph nodes, cutaneous or subcutaneous tumors (non-hepatic lesions). It is mandatory that administration into liver lesions is by image guided injection (either by US or CT scan). Image guidance may also be used for other non-hepatic intratumoral injections but is not required if the lesion is easily visible or palpable. The concentration of talimogene laherparepvec (10^7 or 10^8 PFU/mL) to be administered in Part 2 will be determined on completion of the combination treatment, Cohorts 5 and 6, in Part 1. Talimogene laherparepvec will be used at a maximum volume of 8 mL (established from monotherapy Cohort 3 in Part 1). No intrasubject concentration or volume escalation is allowed. Investigators are encouraged to use the maximum amount whenever lesions allow. Dose reduction for adverse events is not allowed. However, if in the course of administration of talimogene laherparepvec the subject cannot tolerate the full volume 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 to be injected into the tumor(s) depends on the longest diameters of the tumor(s) and necrotic core of the tumor(s) (if applicable) and should be dosed according to the injection volume guideline in Table 3.

Liver Lesions with Necrotic Cores

As of Protocol Amendment 6 (dated 26 October 2021), intrahepatic injections of talimogene laherparepvec and liver biopsies are no longer performed in this study. Liver lesions with a necrotic core contain less viable cancer cells for talimogene laherparepvec to infect. Thus, there are two separate dosing guidelines depending on whether there is a significantly sized necrotic core (the longest diameter of the necrotic

core is ≥ 75% of the longest diameter of the tumor) or not (Table 3). When determining the percent of the tumor diameter that is necrotic, measurements from the most recent multiphase CT or MRI should be used. However, the longest diameters of tumors assessed by US or CT in preparation for injection guidance of each treatment should be used to determine the maximum injection volumes from Table 3. Talimogene laherparepvec should not be injected directly into necrotic tissue and should be administered into viable tissue. Tumors which do not have a large enough non-necrotic portion to reliably inject should not be injected with talimogene laherparepvec regardless of the overall tumor size.

Table 3. Talimogene Laherparepvec Liver Injection Volume Guideline

Part 1: Cohorts 1, 2, 5 and 6[a]		
Individual Tumor Diameter[b]		
< 75% necrotic tumor diameter[c]	≥ 75% necrotic tumor diameter[c]	Maximum Injection Volume
≥ 4 cm	≥ 5 cm	4 mL
≥ 2 to < 4 cm	≥ 2.5 to < 5 cm	2 mL
< 2 cm	< 2.5 cm	1 mL
Part 1: Cohort 3 and 4[a]		
Individual Tumor Diameter[b]		
< 75% necrotic tumor diameter[c]	≥ 75% necrotic tumor diameter[c]	Maximum Injection Volume
≥ 8 cm	≥ 10 cm	8 mL
≥ 6 to < 8 cm	≥ 7.5 to < 10 cm	6 mL
≥ 4 to < 6 cm	≥ 5 to < 7.5 cm	4 mL
≥ 2 to < 4 cm	≥ 2.5 to < 5 cm	2 mL
< 2 cm	< 2.5 cm	1 mL

[a] One of the two injection volume guidelines above will be used for each Group in Part 2
[b] Longest tumor diameter assessed by ultrasound or CT in preparation for injection guidance
[c] Based on longest necrotic core diameter divided by longest tumor diameter from most recent multiphase Computed Tomography or Magnetic Resonance Imaging

Excluded liver lesions for injection: any lesions < 1 cm from the hepatic capsule (bleeding risk) or the right main, left main, or common hepatic bile ducts (biliary obstruction risk).

Any lesion selected for injection must not be located, in the Investigator's opinion, where any potential tumor swelling after injection may lead to significant morbidity or obstruction or where there may be significant risk of bleeding.

When biopsies of lesions are scheduled on treatment days (Table 8), they should occur prior to injection of talimogene laherparepvec. When injecting liver lesions, only lesions that have been visualized on CT or MRI multiphase scans used for tumor assessments may be injected. New lesions that have appeared on injection guidance CT scans or US between tumor assessments CT or MRI scans, may not be injected until they have been visualized on tumor assessment CT or MRI scans. All reasonably injectable lesions should be injected with the maximum dosing volume available on an individual dosing occasion (Table 3 and Table 4).

For cutaneous, subcutaneous or superficial nodes, calipers or ruler can be used to measure lesions for injection.

Table 4. PART 2 Only: Talimogene Laherparepvec Injection Volume Guideline Based on Tumor Size for Cutaneous, Subcutaneous and Nodal Lesions

Tumor Size (longer dimension)	Maximum Injection Volume
≥ 10 cm[a]	8.0 mL
≥ 7.5 to < 10 cm[a]	6.0 mL
≥ 5.0 cm to < 7.5 cm[b]	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

[a] Volumes > 4.0 mL are only to be used if 8.0 mL is the MTV determined from Part 1 and is allowed in Part 2.
[b] If the MTV from Part 1 is determined to be 4 mL, then maximum volume for lesions ≥ 5 cm, including those ≥ 7.5 cm, is 4.0 mL.

On each treatment day, prioritization of injections is recommended as follows:

Part 1:

- **As of Protocol Amendment 6 (dated 26 October 2021), intrahepatic injections of talimogene laherparepvec and liver biopsies are no longer performed in this study.** Any new injectable liver tumor that has appeared on tumor assessment CT or MRI scans since the start of treatment (from newest to oldest). New liver lesions that appear between tumor assessments scans on the CT scans or US used for needle guidance should not be injected until they have been imaged and measured on tumor assessment CT or MRI scans. Lesion selected for injection must not be located, in the Investigator's opinion, where any potential tumor swelling after

injection may lead to significant morbidity or obstruction or where there may be significant risk of bleeding.

- By tumor size, beginning with the largest liver tumor.
- Any previously uninjectable liver tumor(s) that are now large enough to inject.

Part 2:

- **As of Protocol Amendment 6 (dated 26 October 2021), intrahepatic injections of talimogene laherparepvec and liver biopsies are no longer performed in this study.** Any new injectable cutaneous or sub-cutaneous lesion or superficial lymph node that has appeared since the last injection or any new injectable liver lesion that has appeared on tumor assessment CT or MRI scan since the start of treatment (newest to oldest). New liver or deep lymph node lesions that appear between tumor assessments scans on the CT scans or US used for needle guidance should not be injected until they have been imaged and measured on tumor assessment CT or MRI scans. Lesion selected for injection must not be located, in the Investigator's opinion, where any potential tumor swelling after injection may lead to significant morbidity or obstruction or where there may be significant risk of bleeding.
- By tumor size, beginning with the largest tumor.
- Any previously uninjectable tumor(s) that are now large enough to inject.

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 injection volume guideline based on tumor size per Table 3 and Table 4 as applicable. Volumes of less than 0.05 mL should not be planned for administration into a lesion. Lesions should be injected until the maximum volume per day (either 4 or 8 mL) has been reached, or there are no further injectable lesions, whichever comes first. In Part 1, subjects must be monitored in the hospital for 23 hours after each injection for the first 3 cycles of talimogene laherparepvec before discharge to home. The observation period may be reduced, at the investigator's discretion, to a minimum of 6 hours after each injection for cycles 4 onwards In Part 2, subjects receiving intrahepatic injections must be monitored for a minimum of 6 hours after each talimogene laherparepvec injection. Subjects who do not receive an intrahepatic injection of talimogene laherparepvec but receive only, cutaneous, subcutaneous, or nodal injections must be monitored for a minimum of 1 hour after each talimogene laherparepvec injection, including vital signs. Monitoring should continue if there are any signs of clinical deterioration.

Subjects will be treated with talimogene laherparepvec until a CR is achieved, all injectable tumors have disappeared, confirmed PD per modified irRC-RECIST, intolerance of study treatment, until they have received 6 cycles and in the investigator's

opinion no further talimogene laherparepvec injection would be of clinical benefit, or the investigator determines it is in the best interest of the subject to discontinue treatment (eg, rapid clinical deterioration or worsening symptomatic disease requiring alternative systemic anti-cancer therapy), whichever occurs first. After 6 cycles have been received, the subject may be a candidate for up to 6 additional cycles of talimogene laherparepvec (Section 3.1.3). In Part 2, if the subject has completed 12 cycles of talimogene laherparepvec, the subject may be a candidate for additional cycles of talimogene laherparepvec, up to a total of 35 cycles, if there are still **cutaneous, subcutaneous, or nodal** lesions suitable for injection provided that in the opinion of the investigator, the subject has clinical benefit and provided sponsor medical monitor approval has been obtained by the investigator. Due to the mechanism of action of talimogene laherparepvec, 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-RECIST (Appendix D) and is able to tolerate treatment. In Part 2, in the event that talimogene laherparepvec was discontinued for reasons other than toxicity (e.g., no further injectable lesion), and subject subsequently developed progressive disease or injectable disease while still on pembrolizumab, talimogene laherparepvec may be resumed if investigator and medical monitor are in agreement. If the liver is to be injected, subjects must be monitored for a minimum of 6 hours after each talimogene laherparepvec injection.

The concentration, start date, volume, and lot number of talimogene laherparepvec are to be recorded on the CRF.

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

Dose concentration reductions of talimogene laherparepvec are not permitted. However, a reduction in the volume injected due to a disease response is permitted.

For subjects that have an INR of > 1.5 or platelet $< 50{,}000/mm^3$ ($50 \times 10^9/L$) prior to injection, talimogene laherparepvec administration should be delayed until INR is ≤ 1.5 or platelet $\geq 50{,}000/mm^3$ ($50 \times 10^9/L$) without transfusion. Any planned correction of INR or platelet count with transfusion prior to injection should be first discussed and approved with the sponsor medical monitor.

If a subject experiences any of the following treatment-related toxicities, talimogene laherparepvec administration should be delayed until the toxicity has resolved to at least CTCAE version 4.03 grade 1:

- 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 toxicity
- any grade 3 or higher non-hematologic laboratory value unless deemed not clinically important per both investigator and sponsor.

For hepatotoxicity stopping rules refer to Section 6.4.

If a subject requires corticosteroid dosing of $>$ 10 mg prednisone daily (or equivalent, eg, 1.5 mg dexamethasone) for any reason, talimogene laherparepvec and pembrolizumab dosing must be held until the corticosteroid dose has decreased to $\leq$ 10 mg prednisone daily (or equivalent).

All necessary supportive care shall be available to subjects except for those listed in Section 6.9. Talimogene laherparepvec treatment should be continued based on the potential risk/benefit assessment of the subject.

If talimogene laherparepvec treatment was delayed by $>$ 2 weeks, that dose will be deemed to have been missed and the subject will proceed to the next scheduled treatment visit.

If talimogene laherparepvec dosing is delayed by more than 6 weeks from the date of the planned dose (ie, approximately 9 weeks from the previous dose) due to the occurrence of an adverse event that is considered related to talimogene laherparepvec, the subject must be permanently taken off talimogene laherparepvec treatment.

If talimogene laherparepvec dosing is delayed by more than 6 weeks from the date of the planned dose (ie, approximately 9 weeks 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 is to be permanently discontinued for subjects meeting any of the following criteria:

- Subject developed a DLT during the DLT evaluation period (please refer to Section 3.1.4.3).

- The subject, for any reason, requires treatment with another anti-cancer therapeutic agent for treatment of the study disease (other than the exceptions noted in Section 6.6). In this case, discontinuation from the treatment occurs immediately upon introduction of the new agent.
- Confirmed PD occurs as defined per modified irRC-RECIST (Appendix D).
- 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 6 weeks from the date of the planned dose (ie, approximately 9 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 6 weeks from the date of the planned dose (ie, approximately 9 weeks from the previous dose).
- 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.

Dosing should be permanently discontinued if, in the opinion of the investigator, the subject develops clinical evidence of any serious herpes infection (such as HSV hepatitis, encephalitis, or disseminated infection). Systemic anti-herpetic drugs (eg, acyclovir, valacyclovir, or famciclovir) should only be reserved for suspected cases of severe herpetic infection as outlined in the Guidelines for Suspected Serious Herpetic Infections document, but topically administered anti-herpetic drugs may be administered for limited suspected herpetic skin lesions after they are swabbed and tested for talimogene laherparepvec using qPCR.

For Part 1 Group A Cohorts 1-6, Part 1 Group B Cohorts 5 and 6a, and Part 2 Arms I-VI, in subjects with history of HBV and HCV, viral load should be rechecked when ALT or AST are elevated more than twice their baseline value. If reactivation of HBV or HCV is confirmed, discontinuation of talimogene laherparepvec and starting hepatitis antiviral medication should be considered after consultation with the sponsor medical monitor.

For Part 1 Group B Cohort 6b and Part 2 Group B Arm VI subjects with well-controlled viral hepatitis, please see Table 15. Subjects who discontinue talimogene laherparepvec are to continue to return for all other study procedures and

measurements including the 30-day safety follow-up visit (ie, until approximately 30 [+ 7] days after the last dose of study drug) and long term survival follow-up.

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 IV infusion.

Additional details regarding pembrolizumab are provided in the IPIM.

6.2.2.1 Pembrolizumab Dosage, Administration, and Schedule

The Pembrolizumab treatment to be used in this trial is outlined in Table 5 below.

Table 5. Pembrolizumab Trial Treatment

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen	Use
Pembrolizumab	200 mg	Every three weeks	Intravenous	Day 1 of each cycle (3 week cycles)	Experimental

Pembrolizumab should begin on the day of enrollment or as close as possible to the date on which the subject is allocated/assigned.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of trial treatments in accordance with the protocol and any applicable laws and regulations.

Trial treatment of pembrolizumab will be administered on Day 1 of each 3-week treatment cycle after all procedures and assessments have been completed as detailed in the Schedule of Assessments (Table 10 and Table 13).

Pembrolizumab will be administered as a dose of 200 mg using a 30-minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes - 5 min/+10 min).

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

[redacted]

6.2.2.2 Dosage Modification and Toxicity Management Guidelines for Pembrolizumab

6.2.2.2.1 Dose Modification and Toxicity Management for Immune-related Adverse Events Associated With Pembrolizumab

Adverse events associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related adverse events may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical trial data, most immune-related adverse events were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected immune-related adverse events, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of immune-related adverse events, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for immune-related adverse events associated with pembrolizumab are provided in Table 6. See Section 6.2.2.3 for supportive care guidelines, including use of corticosteroids.

Table 6. Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated With Pembrolizumab

General instructions:

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

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.03)	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 to 2 mg/kg prednisone or equivalent) followed by taper Add prophylactic antibiotics for opportunistic infections	Monitor subjects for signs and symptoms of pneumonitis Evaluate subjects with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	Monitor subjects 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). Subjects with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. Subjects with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

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Table 6. Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated With Pembrolizumab

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.03)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
AST / ALT elevation or Increased bilirubin	Grade 2[a]	Withhold	Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3[b] or 4[c]	Permanently discontinue	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold[d]	Initiate insulin replacement therapy for subjects with T1DM Administer antihyperglycemic in participants with hyperglycemia	Monitor subjects for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated.	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[d]		
Hyperthyroidism	Grade 2	Continue	Treat with nonselective beta-blockers (e.g., propranolol) or thionamides as appropriate	Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[d]		

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Table 6. Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated With Pembrolizumab

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.03)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Hypothyroidism	Grade 2, 3 or 4	Continue	Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care.	Monitor for signs and symptoms of thyroid disorders.
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper.	Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All other irAEs	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[e].		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

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

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.
[a] AST/ALT: > 3.0 to 5.0 x ULN if baseline normal; > 3.0 to 5.0 x baseline, if baseline abnormal; bilirubin: > 1.5 to 3.0 x ULN if baseline normal; > 1.5 to 3.0 x baseline if baseline abnormal
[b] AST/ALT: > 5.0 to 20.0 x ULN, if baseline normal; > 5.0 to 20.0 x baseline, if baseline abnormal; bilirubin: > 3.0 to 10.0 x ULN if baseline normal; > 3.0 to 10.0 x baseline if baseline abnormal
[c] AST/ALT: > 20.0 x ULN, if baseline normal; > 20.0 x baseline, if baseline abnormal; bilirubin: > 10.0 x ULN if baseline normal; > 10.0 x baseline if baseline abnormal
[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.
[e] Events that require discontinuation include but are not limited to: encephalitis and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

6.2.2.2.2 Dose Modification and Toxicity Management of Infusion-reactions Related to Pembrolizumab

Pembrolizumab may cause severe or life threatening infusion-reactions 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 7.

Table 7. Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines

CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hrs	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment	Subject may be premedicated 1.5 hr (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).

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Table 7. Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines

CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4	Stop Infusion.	No subsequent dosing
Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Additional appropriate medical therapy may include but is not limited to: • Epinephrine** • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids	
Grade 4: Life-threatening; pressor or ventilatory support indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Subject is permanently discontinued from further study drug treatment.	

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CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; NSAIDs = Nonsteroidal anti-inflammatory drugs; PO = oral

[a] 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 v4.03 (CTCAE) at http://ctep.cancer.gov

6.2.2.2.3 Other Allowed Dose Interruption for Pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related adverse events such as medical / surgical events or logistical reasons not related to study therapy. 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 subject's study record.

6.2.2.3 Supportive Care Guidelines for Pembrolizumab

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined along with the dose modification guidelines in Section 6.2.2.2, (Table 6). Where appropriate, these guidelines include the use of oral or IV 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 of the event, it is determined not to be related to pembrolizumab, the Investigator does not need to follow the treatment guidance. Refer to in Section 6.2.2.2, for guidelines regarding dose modification and supportive care.

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

6.2.2.4 Diet and Other Considerations While Taking Pembrolizumab

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

6.3 Other Protocol-required Therapies

All other protocol-required therapies including, topical anesthetic or injectable local anesthetic medications used for pretreatment of the talimogene laherparepvec injection site and oral or systemic steroids for management of pembrolizumab immune related adverse events, that are commercially available are not provided 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 Hepatotoxicity Stopping and Rechallenge Rules

Subjects with abnormal hepatic laboratory values (ie, ALP, AST, ALT, TBL) and/or INR and/or signs/symptoms of hepatitis (as described in Sections 6.4.1 and 6.4.2) may meet the criteria for withholding or permanent discontinuation of Amgen investigational

product as specified in the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009. Refer to Section 9.2.5.1 for management of hepatic events of clinical interest associated with pembrolizumab.

6.4.1 Criteria for Permanent Discontinuation of Talimogene Laherparepvec Due to Potential Hepatotoxicity

Talimogene laherparepvec should be discontinued permanently and the subject should be followed according to the recommendations in Appendix E (Drug-induced Liver Injury Reporting and Additional Assessment) for possible drug-induced liver injury (DILI), if ALL of the criteria below are met:

- Current TBL > 2x ULN following baseline TBL < ULN or INR > 1.5
- AND Current AST or ALT > 3x ULN following baseline AST or ALT < ULN, respectively
- AND no other cause for the combination of the above laboratory abnormalities is immediately apparent (ie, dosing should not continue while awaiting the results of pending investigations); important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:

Hepatobiliary tract disease

Viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, HSV excluding talimogene laherparepvec, varicella, toxoplasmosis, and parvovirus)

Right sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia

Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants and mushrooms

Heritable disorders causing impaired glucuronidation (eg, Gilbert's Syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)

Alpha-one antitrypsin deficiency

Alcoholic hepatitis

Autoimmune hepatitis

Wilson's disease and hemochromatosis

Nonalcoholic fatty liver disease including steatohepatitis (NASH)

Non-hepatic causes (eg, rhabdomyolysis, hemolysis)

Please refer to the Guidelines for Suspected Serious Herpetic Infections for conditions where talimogene laherparepvec may be suspected as a cause of hepatitis and for further management.

6.4.2 Criteria for Conditional Withholding of Talimogene Laherparepvec Due to Potential Hepatotoxicity

For subjects who do not meet the criteria for permanent discontinuation of talimogene laherparepvec outlined above, talimogene laherparepvec should be withheld if ANY of the following criteria are met, and the subject should be evaluated for DILI:

- Elevation of either AST or ALT according to the following schedule:

Baseline AST or ALT value	AST or ALT elevation
≤ 3 x ULN	> 5 x ULN for ≥ 2 weeks
≤ 3 x ULN	> 5 x ULN and unable to adhere to enhanced monitoring schedule
≤ 5 x ULN	> 8 x ULN at any time

- or: TBL > 3 x ULN at any time
- or: ALP > 8 x ULN at any time

Talimogene laherparepvec should be withheld pending investigation into alternative causes of DILI. If talimogene laherparepvec is withheld, the subject is to be followed according to recommendations in Appendix E (Drug-induced Liver Injury Reporting and Additional Assessment) for possible DILI. Re-challenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBL, is discovered and the laboratory abnormalities resolve to normal or baseline.

Please refer to the Guidelines for Suspected Serious Herpetic Infections for conditions where talimogene laherparepvec may be suspected as a cause of hepatitis and for further management.

6.4.3 Criteria for Rechallenge of Amgen Investigational Product and Other Protocol-required Therapies After Potential Hepatotoxicity

The decision to re-challenge the subject should be discussed and agreed upon unanimously between the subject and investigator, and between the investigator and Amgen Medical Monitor.

If signs or symptoms recur with re-challenge, then talimogene laherparepvec should be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Section 6.4.1) should not be re-challenged without consulting the Amgen Medical Monitor.

Pembrolizumab should be permanently discontinued for pembrolizumab-related Grade 3 or 4 increase in AST or ALT with no further rechallenge. If there is another etiology for

the AST or ALT elevation, rechallenge with pembrolizumab may only occur with approval of the medical monitor.

6.5 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 6.9.

All prescription and nonprescription concomitant medication administered from the signing of the main informed consent, on an ongoing basis at enrollment, 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 until approximately 30 (+7) days after the last dose of talimogene laherparepvec or pembrolizumab, whichever is later. 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.

6.6 Other Treatment Procedures

As of Protocol Amendment 6 (dated 26 October 2021), intrahepatic injections of talimogene laherparepvec and liver biopsies are no longer performed in this study.

Treatment with talimogene laherparepvec and pembrolizumab in the combination setting may result in the reduction of tumor burden such that surgical resection of previously unresected lesion becomes possible. 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 liver lesions for tumor analysis during study. In the event of a CR, any residual target lesions must be documented by representative biopsy to not contain viable tumor. If a subject undergoes resection of the lesion in the event other than CR, the investigator or designee should notify the sponsor medical monitor and the procedure should be recorded in the source document and CRF. In these instances, if the response of other lesions is at least PR (if other lesions remain), the response should be designated PR with the date of surgery as the date of response. If no residual disease remains following surgery, this should also be noted in the CRF, the response definition again being PR if viable cancer was noted in the surgical

specimen, and CR if no viable cancer was identified in the surgical specimen. Best response of CR or PR due to surgeries will not be considered for assessment of ORR or BOR.

Palliative surgery for relief of symptoms is allowed. Treatment with talimogene laherparepvec and/or pembrolizumab should be held, and the investigator or designee should notify the sponsor as soon as possible. Subjects may be allowed to remain on study after discussion between the sponsor medical monitor and the investigator. Investigator must get approval from the sponsor medical monitor before resuming talimogene laherparepvec and/or pembrolizumab.

Local palliative radiation treatment for relief of various symptoms, including but not limited to bleeding or pain associated with the underlying disease will be permitted at any time during the study. Subjects with local symptoms suggestive of disease progression should be evaluated for tumor response per modified irRC-RECIST (see Appendix D) prior to the administration of palliative radiotherapy. If a subject undergoes local radiation, the investigator or designee should notify the sponsor medical monitor as soon as possible and the treatment should be recorded in the source document and CRF.

If a subject demonstrates evidence of new or worsening CNS metastases, talimogene laherparepvec and/or pembrolizumab treatment 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 medical monitor and the investigator to determine the appropriateness of treatment resumption provided CNS lesions can be treated with stereotactic radiotherapy (including Gamma Knife), whole brain radiation, or craniotomy and if there is no change in the baseline ECOG performance status. Subjects may be allowed to resume talimogene laherparepvec treatment per Section 6.2.1 following treatment of CNS metastases while receiving dexamethasone or a similar corticosteroid at no more than 1.5 mg dexamethasone (or 10 mg prednisone) per day. If higher doses of corticosteroid are used, talimogene laherparepvec must be held until that dose level is reached during the period of steroid tapering.

If a subject with confirmed PD (ie, two consecutive tumor assessments at least 4 weeks [28 days] apart demonstrating PD) 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.

6.7 Medical Devices

Non-investigational medical devices may be used in the conduct of this study as part of standard care.

Non-Amgen non-investigational medical devices (eg, 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.

6.8 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) after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material.

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.

6.9 Excluded Treatments and/or Procedures During Study Period

Subjects must not use any of the following therapies during screening or treatment period (including retreatment for post-CR relapse) of this trial:

- investigational agents (other than pembrolizumab and talimogene laherparepvec) or procedures
- warfarin. Other anticoagulants (ie. low molecular weight heparins, non-steroidal anti-inflammatory drugs) that do not prolong the PT/INR may be administered after investigator discussion with the sponsor and as long as there is adherence to institutional guidelines requiring their withholding for interventional radiology procedures.
- concurrent experimental or approved anti-tumor therapies or biological therapy other than study drug and radiation therapy required for palliation (as noted in Section 6.5)

Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be considered on an exceptional case by case basis after consultation with Sponsor. The subject must have clear measurable disease outside the radiated field. Administration of palliative radiation therapy will be considered clinical progression for the purposes of determining PFS.

- immunotherapy not specified in this protocol
- chemotherapy not specified in this protocol

- chronic oral or systemic steroid medication use at a dose of >10 mg/day of prednisone (1.5 mg/day dexamethasone) or equivalent (with the exception of treatment for adverse events [see Section 6.2.1.2] and CNS metastases [see Section 6.5]). Steroids with low systemic absorption [eg, triamcinolone hexacetonide] injected into a joint space, and intermittent use of steroid inhalers or topical steroid is allowed).
- antiherpetic drugs, except those topically administered
- live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, Bacillus Calmette-Guerin (BCG), and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (eg, Flu - Mist®) are live attenuated vaccines, and are not allowed.
- any surgery for cancer (other than the exceptions noted in Section 6.6)
- Subjects must not schedule any elective non-cancer-related surgeries during the treatment period and for at least 30 days after the last administration of study drug. If a subject undergoes any unexpected surgery during the course of the study, study treatment must be withheld and the investigator or designee should notify the sponsor medical monitor as soon as possible. A subject may be allowed to resume study drug if both the investigator and sponsor medical monitor agree to restart study therapy.
- Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

7. STUDY PROCEDURES

7.1 Schedule of Assessments

The schedule of the assessments for the study is summarized in Table 8 through Table 13.

Refer to the applicable supplemental laboratory manuals for detailed collection and handling of laboratory samples.

Table 8. Schedule of Assessments for Talimogene Laherparepvec Monotherapy Part 1

Study Procedures	Screening			Study Treatment[d] (week/cycle number)																		Follow-up	
	≤ 28 days[a]	≤ 10 days[b]	≤ 72 hour[c]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	Safety[e]	Survival[f]
				Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6				
General Assessments																							
Informed Consent	X																						
Review of Eligibility Criteria	X																						
Demographics	X																						
Medical and Surgical History	X																						
Vital Signs[g,w]	X			X			X			X			X			X			X			X	
Physical Exam	X			X																		X	
Weight	X			X			X			X			X			X			X			X	
ECOG Performance Status	X			X			X			X			X			X			X			X	
12-lead ECG	X																					X	
Child-Pugh Score	X																					X	
Recording of Concomitant Medication[h]	X →																					X	X[i]
Review of DREs, AEs and SAEs[h]	X →																					X	X
Survival Assessment																							X
Local Laboratory Tests																							
Chemistry[j]		X		X	X	X	X	X	X	X	X		X			X			X			X	
Hematology[j]		X		X	X	X	X	X	X	X	X		X			X			X			X	
Coagulation (PT/INR and PTT or aPTT)[j]		X		X	X	X	X	X	X	X	X		X			X			X			X	
Urine or Serum Pregnancy Test[k]			X																			X	
Disease Specific Assessments[l]	X																						
Serum LDH[m]		X											X									X	
Hepatitis B and C Testing[n]		X																				X	
CEA (CRC and GEC Adenocarcinoma Subjects Only)[m]		X											X									X	
AFP (HCC Subjects Only)[m]		X											X									X	
CA 19-9 (GEC, CRC, and HCC Only)[m]		X											X									X	

Footnotes and abbreviations are defined after Table 9 below

Table 8. Schedule of Assessments for Talimogene Laherparepvec Monotherapy Part 1

Study Procedures	Screening			Study Treatment[d] (week/cycle number)																		Follow-up	
	≤ 28 days[a]	≤ 10 days [b]	≤ 72 hour [c]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	Safety[e]	Survival[f]
				Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6				
Central Laboratory Tests																							
HSV-1 IgG Antibody Serostatus				X						X												X	
[redacted]																							
Blood and Urine for qPCR[q]				X	X	X	X	X	X	X	X		X									X	
Swab of Injection Site Surfaces and Occlusive Dressings[r]				X	X	X	X	X	X	X	X		X										
Swab of Oral Mucosa[s]				X	X	X	X	X	X	X	X		X			X			X			X	
Swab of Herpetic Lesion for qPCR[t]				Within 3 days of occurrence of suspected lesion of herpetic origin																			
Radiographic Tumor/Response Assessments																							
Radiographic (CT, PET/CT, or MRI) Scans & Tumor Assessment [u]	X												X									X	X
Optional liver ultrasound[v]		X																					
Treatment Administration																							
Talimogene Laherparepvec[w]				X			X			X			X			X			X [w]				
Post-treatment Observation[x]				X			X			X			X			X			X				
Reporting Exposure to Talimogene Laherparepvec																							
Exposure of Subject's Household member or Caregiver[y]				→																			
Exposure of Subject's Healthcare Provider[y]				→																			
[redacted]																							

Footnotes and abbreviations are defined after Table 9 below

Table 9. Schedule of Assessments for Talimogene Laherparepvec Monotherapy: Post Cycle 6

	Study Treatment[d] (week/cycle number)																		Follow-up	
Study Procedures	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	Safety[e]	Survival[f]
	Cycle 7			Cycle 8			Cycle 9			Cycle 10			Cycle 11			Cycle 12				
GENERAL ASSESSMENTS																				
Informed Consent																				
Review of Eligibility Criteria																				
Demographics																				
Medical and Surgical History																				
Vital Signs[g,x]	X			X			X			X			X			X			X	
Physical Exam	X																		X	
Weight	X			X			X			X			X			X			X	
ECOG Performance Status	X			X			X			X			X			X			X	
12-lead ECG																			X	
Child-Pugh Score																			X	
Recording of Concomitant Medication[h]		→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	X[i]
Review of DREs, AEs and SAEs[h]		→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	X
Survival Assessment																				X
LOCAL LABORATORY TESTS																				
Chemistry[j]	X			X			X			X			X			X			X	
Hematology[j]	X			X			X			X			X			X			X	
Coagulation (PT/INR and PTT or aPTT)[j]	X			X			X			X			X			X			X	
Urine or Serum Pregnancy Test[k]																			X	
Serum LDH[l]	X									X									X	
Hepatitis B and C Testing[n]																			X	
CEA (CRC and GEC Adenocarcinoma Subjects Only)[l]	X									X									X	
AFP (HCC Subjects Only)[l]	X									X									X	
CA 19-9 (GEC , CRC, and HCC Only)[l]	X									X									X	

Footnotes and abbreviations are defined after Table 9 below

Table 9. Schedule of Assessments for Talimogene Laherparepvec Monotherapy: Post Cycle 6

Study Procedures	Study Treatment[d] (week/cycle number)																		Follow-up	
	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	Safety[e]	Survival[f]
	Cycle 7			Cycle 8			Cycle 9			Cycle 10			Cycle 11			Cycle 12				
CENTRAL LABORATORY TESTS																				
HSV-1 IgG Antibody Serostatus																			X	
[redacted]																				
Blood and Urine for qPCR[q]																			X	
Swab of Oral Mucosa[s]	X			X			X			X			X			X			X	
Swab of Herpetic Lesion for qPCR[q,t]	Within 3 days of occurrence of suspected lesion of herpetic origin																			
RADIOGRAPHIC TUMOR/RESPONSE ASSESSMENTS																				
Radiographic (CT, PET/CT, or MRI) Scans & Tumor Assessment[u]	X									X									X	X
TREATMENT ADMINISTRATION																				
Talimogene Laherparepvec[w]	X			X			X			X			X			X				
Post-treatment Observation[x]	X			X			X			X			X			X				
REPORTING EXPOSURE TO TALIMOGENE LAHERPAREPVEC																				
Exposure of Subject's Household member or Caregiver[y]		→																		
Exposure of Subject's Healthcare Provider[y]		→																		
[redacted]																				

AE = adverse event; AFP = alpha fetoprotein; aPTT = activated partial thromboplastin time; CA 19-9 = cancer antigen 19-9; CEA = carcinoembryonic antigen; CRC = colorectal adenocarcinoma; CRF = case report form; CT = computed tomography; DRE = disease related event; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; GEC = gastroesophageal cancer (adenocarcinoma or squamous cell carcinoma); HCC = hepatocellular carcinoma; HSV-1 = herpes simplex virus type 1; IgG = imunoglobulin G; INR = international normalization ratio; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; PET = positron emission tomography; PT = prothrombin time; PTT = partial thromboplastin time; qPCR = real-time polymerase chain reaction; SAE = serious adverse event

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

[b] Procedures to be performed ≤ 10 days prior to enrollment.

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

[d] During treatment, assessments and procedures will be performed within ± 3 days of the planned visit, unless otherwise specified.

[e] Safety follow-up will be performed approximately 30 (+ 7) days after the last dose of talimogene laherparepvec.

[f] Subjects will be followed for survival by clinic visit or telephone contact approximately every 12 weeks ± 28 days from the date of the safety follow-up visit until up to approximately 24 months after the date of last subjects enrolled in Part 1. Subsequent anti-cancer treatments will be collected as part of the long-term follow-up survival assessment.

[g] Vital signs (blood pressure, resting heart rate, respiration rate, and temperature) must be performed prior to each talimogene laherparepvec administration.

[h] All serious adverse events, follow up to a serious adverse event, including death due to any cause that occur after the subject has signed the main informed consent through 90 (+7) days after the last administration of talimogene laherparepvec, 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 case report form. In addition, all serious adverse events that occur during the long-term safety follow-up period until the end of study are to be reported to Amgen and recorded in the CRF. As described in Section 9.2.3.2, there is no requirement to monitor study subjects for serious adverse events following the protocol required reporting period (as defined in Section 9.2.3) or after the end of study. However, these serious adverse events should be reported to Amgen (regardless of causality) if the investigator becomes aware of them (per regional regulatory requirements). All serious adverse events must be submitted to Amgen within 24 hours following the investigator's awareness of the event via the applicable CRF. All disease related events and nonserious adverse events that occur and concomitant medications that are administered after the subject has signed the main informed consent through 30 (+7) days after the last administration of talimogene laherparepvec will be recorded in the events CRF.

[i] Only subsequent anti-tumor treatment will be recorded.

[j] During treatment blood samples for chemistry, hematology and coagulation panels will be collected weekly for the first 8 weeks of treatment and then prior to each talimogene laherparepvec administration until end of study treatment.

[k] Urine or serum pregnancy test to be performed on female of childbearing potential. Additional on-treatment pregnancy testing may be performed at the investigator's discretion or as defined in a county-specific protocol supplement at the end of the Appendix Section of the protocol as required per local laws and regulations.

[l] Disease specific assessments will only be performed on archived tissue (preferred) or screening biopsy tissue if results from previous testing are not available. Results should be submitted during screening and any time after enrollment. For details and a list of disease specific assessments refer to Section 7.2.1.

[m] During treatment blood samples for lactate dehydrogenase (LDH), carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP),and cancer antigen 19-9 (CA 19-9) will be collected at screening and at week 10 (± 1 week) and then every 9 weeks (± 1 week) prior to talimogene laherparepvec administration until end of study treatment.

[n] Hepatitis C and B panel should be performed at screening if serology has not been performed previously. Subjects who are positive for hepatitis B virus (HBV) and hepatitis C virus (HCV) infection should receive additional testing of viral load by polymerase chain reaction (PCR) at screening,, and at the safety follow-up. For additional information refer to Section 7.2.1 through 7.2.3.1.

[q] During treatment blood and urine sample for real-time polymerase chain reaction (qPCR) testing of talimogene laherparepvec DNA will be performed at the following time points: on Weeks 1 and 4 prior to talimogene laherparepvec administration and approximately 1 hour (± 15 minutes), 4 hours (± 30 minutes), 8 hours (± 1 hour), 24 (± 4) hours, 48 (± 4) hours, 7 days (± 2 days), and 14 days (± 2 days) following talimogene laherparepvec administration; on Week 7 prior to talimogene laherparepvec administration and 7 days (± 2 days) following talimogene laherparepvec administration; on week 10 prior to talimogene laherparepvec administration; and at safety follow-up visit.

[r] Swabs of the surface of the injection sites and exterior of occlusive dressings for qPCR testing of talimogene laherparepvec DNA with or without 50% Tissue Culture Infective Dose (TCID50) assay of talimogene laherparepvec virus. During treatment the surface of the injection site will be swabbed at the following timepoints: on Weeks 1 and 4 prior to talimogene laherparepvec administration and 24 (± 4) hours, 48 (± 4) hours, 7 (± 2) days, and 14 (± 2) days following talimogene laherparepvec administration; on Week 7 prior to talimogene laherparepvec administration and 7 (± 2 days) following talimogene laherparepvec administration; and on Week 10 prior to talimogene laherparepvec administration. During treatment the exterior surface of the injection site dressings will be swabbed at the following timepoints: 24 (± 4) hours and 48 (± 4) hours after Week 1 and 4 talimogene laherparepvec administration and 7 (± 2) days after Week 1, 4, and 7 talimogene laherparepvec administrations.

[s] Swabs of oral mucosa: During treatment swabs of oral mucosa for qPCR testing of talimogene laherparepvec DNA with or without TCID50 assay for talimogene laherparepvec virus will be collected at the following visits: Week 1 and 4 prior to talimogene laherparepvec administration and 7 (± 2) days and 14 (± 2) days following talimogene laherparepvec administration; Week 7 prior to talimogene laherparepvec administration and 7 (± 2) days following talimogene laherparepvec administration; Week 10 and subsequent cycles prior to each talimogene laherparepvec administration. During safety follow-up, swabs of oral mucosa will be collected at the 30 (+7) day safety follow-up visit for qPCR testing of talimogene laherparepvec DNA.

[t] Swabs of any lesion suspected to be herpetic in origin (if any) will be collected during treatment and safety follow-up as follows: subject should 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 sent to the central laboratory for detection of talimogene laherparepvec DNA using qPCR testing.

[u] Radiographic tumor imaging: During treatment, radiographic tumor imaging will be performed independent of treatment cycle at week 10 (± 1 week) and then every 9 weeks (± 1 week) until confirmed progressive disease (PD) per modified immune-related response criteria (irRC) simulating RECIST version 1.1 (irRC-RECIST) (Appendix D). Radiographic imaging is required at the safety follow up visit if the subject ended treatment prior to documentation of confirmed PD per modified irRC-RECIST and has not had radiographic tumor imaging performed within 9 weeks (± 1 week) of the visit. Every effort should be made to complete radiographic assessments during the long-term follow-up approximately every 12 weeks (+ 1 week) until documented confirmed PD per modified irRC-RECIST, start of new anticancer treatment, death, or end of study, whichever occurs first, for subjects discontinuing study treatment for any reason other than confirmed PD. Response (complete response [CR], or partial response [PR]) or disease progression to be confirmed by second consecutive radiographic assessments no less than 4 weeks from the date of the first documented response or disease progression. Note: Confirmation of disease progression is required only in the absence of rapid clinical deterioration (ie, rapid decline in performance status) or symptomatic disease requiring rapid initiation of alternative systemic anti-cancer therapy.

[v] To be performed if required by site for assessment of the intrahepatic lesion injection location. **As of Protocol Amendment 6 (dated 26 October 2021), intrahepatic injections of talimogene laherparepvec and liver biopsies are no longer performed in this study.**

[w] If no progression is seen after a total of 6 cycles, up to 6 additional cycles of talimogene laherparepvec, at maximum tolerated dose if known or otherwise previously received dose, every 21 (± 3 days) may be administered, or the subject may proceed to alternative therapies depending on investigator discretion.

[x] All subjects will undergo a 23 hour observation period following the first 3 cycles of talimogene laherparepvec treatment with vital signs (temperature, resting heart rate, systolic and diastolic blood pressure and respiratory rate) recorded every 30 minutes for the first 2 hours, hourly for the next 4 hours, then once every 4 to 6 hours with vital signs also obtained at the end of the observation period. For cycles 4 onwards, the observation period after each dose of talimogene laherparepvec may be reduced to a minimum of 6 hours at the investigator's discretion with vital signs recorded every 30 minutes for the first 2 hours and hourly for the next 4 hours and once at the end of the observational period. The subjects should be hospitalized if there is clinical deterioration during any observation period.

[y] Reporting potential or known unintended exposure to talimogene laherparepvec: 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 signs or symptoms suspected to be herpetic origin or is 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 DNA by qPCR testing in a swab taken from a lesion, if any, in a subject's household member, caregiver, or healthcare provider.

Table 10. Part 1 Schedule of Assessments for Talimogene Laherparepvec and Pembrolizumab Combination Treatment

Study Procedures	Screening			Study Treatment[d] (week/cycle number)																		Follow-up	
	≤ 28 days[a]	≤ 10 days[b]	≤ 72 hour[c]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	Safety[e]	Survival[f]
				Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6				
GENERAL ASSESSMENTS																							
Informed Consent	X																						
Review of Eligibility Criteria	X																						
Demographics	X																						
Medical and Surgical History	X																						
Vital Signs[g,h]	X			X			X			X			X			X			X			X	
Physical Exam	X			X																		X	
Weight	X			X			X			X			X			X			X			X	
ECOG Performance Status	X			X			X			X			X			X			X			X	
12-lead ECG	X																					X	
Child-Pugh Score	X																					X	
Recording of Concomitant Medication[i]	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→		X	X[j]
Review of DREs, AEs and SAEs[i]	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→		X	X
Survival Assessment																							X
LOCAL LABORATORY TESTS																							
Chemistry[k]		X		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			X	
Coagulation (PT/INR and PTT or aPTT)[k]		X		X	X	X	X	X	X	X	X		X			X			X			X	
Thyroid Function Tests (T3, FT3, FT4, TSH)[l]		X		X						X						X						X	
Urine or Serum Pregnancy Test[m]			X																			X	
Disease Specific Assessments[n]	X																						
Serum LDH[o]		X											X									X	
Hepatitis B and C Testing[p]		X								X[q]												X	
CEA (CRC and GEC Adenocarcinoma Subjects Only)[o]		X											X									X	
AFP (HCC Subjects Only)[o]		X											X									X	
CA 19-9 (GEC , CRC, and HCC Only)[o]		X											X									X	

Footnotes and abbreviations after Table 11 below.

Table 10. Part 1 Schedule of Assessments for Talimogene Laherparepvec and Pembrolizumab Combination Treatment

Study Procedures	Screening			Study Treatment[d] (week/cycle number)																		Follow-up	
	≤ 28 days[a]	≤ 10 days[b]	≤ 72 hour[c]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	Safety[e]	Survival[f]
				Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6				
CENTRAL LABORATORY TESTS																							
HSV-1 IgG Antibody Serostatus				X						X												X	
[redacted]																							
Blood and Urine for qPCR[t]				X	X	X	X	X	X	X	X		X									X	
Swab of Injection Site Surfaces and Occlusive Dressings[u]				X	X	X	X	X	X	X	X		X										
Swab of Oral Mucosa[v]				X	X	X	X	X	X	X	X		X			X			X			X	
Swab of Herpetic Lesion for qPCR[w]				Within 3 days of occurrence of suspected lesion of herpetic origin																			
Blood for Anti-Pembrolizumab antibody[x]				X			X						X						X				
Blood for Pembrolizumab PK[y]				X			X						X						X				
Radiographic (CT, PET/CT, or MRI) Scans & Tumor Assessment[z]	X												X									X	X
Optional liver ultrasound[aa]		X																					
TREATMENT ADMINISTRATION																							
Talimogene Laherparepvec[ab]				X			X			X			X			X			X[w]				
Pembrolizumab[ac]				X			X			X			X			X			X				
Post-treatment Observation[h]				X			X			X			X			X			X				
REPORTING EXPOSURE TO TALIMOGENE LAHERPAREPVEC																							
Exposure of Subject's Household member or Caregiver[ad]				→																			
Exposure of Subject's Healthcare Provider[ad]				→																			
[redacted]																							

Footnotes and abbreviations after Table 11 below.

Table 11. Part 1 Schedule of Assessments for Talimogene Laherparepvec and Pembrolizumab Combination Treatment: Post Cycle 6

	Study Treatment[d] (week/cycle number)																			Follow-up	
Study Procedures	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	Pembrolizumab Cycles 7-35	Safety[e]	Survival[f]
	Cycle 7			Cycle 8			Cycle 9			Cycle 10			Cycle 11			Cycle 12					
GENERAL ASSESSMENTS																					
Informed Consent																					
Review of Eligibility Criteria																					
Demographics																					
Medical and Surgical History																					
Vital Signs[g, h]	X			X			X			X			X			X			X	X	
Physical Exam	X																			X	
Weight	X			X			X			X			X			X			X	X	
ECOG Performance Status	X			X			X			X			X			X			X	X	
12-lead ECG																				X	
Child-Pugh Score																				X	
Recording of Concomitant Medication[i]	→																			X	X[j]
Review of DREs, AEs and SAEs[i]	→																			X	X
Survival Assessment																					X
LOCAL LABORATORY TESTS																					
Chemistry[k]	X			X			X			X			X			X			X	X	
Hematology[k]	X			X			X			X			X			X			X	X	
Coagulation (PT/INR and PTT or aPTT)[k]	X			X			X			X			X			X			X	X	
Thyroid Function Tests (T3, FT3, FT4, TSH)[l]	X						X													X	
Urine or Serum Pregnancy Test[m]																				X	
Serum LDH[o]	X									X										X	
Hepatitis B and C Testing[p]																				X	
CEA (CRC and GEC Adenocarcinoma Subjects Only)[o]	X									X										X	
AFP (HCC Subjects Only)[o]	X									X										X	
CA 19-9 (GEC , CRC, and HCC Only)[o]	X									X										X	

Footnotes and abbreviations after Table 11 below.

Table 11. Part 1 Schedule of Assessments for Talimogene Laherparepvec and Pembrolizumab Combination Treatment: Post Cycle 6

	Study Treatment[d] (week/cycle number)																			Follow-up	
Study Procedures	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	Pembrolizumab Cycles 7-35	Safety[e]	Survival[f]
	Cycle 7			Cycle 8			Cycle 9			Cycle 10			Cycle 11			Cycle 12					
CENTRAL LABORATORY TESTS																					
HSV-1 IgG Antibody Serostatus																				X	
[redacted]																					
Blood and Urine for qPCR[t]																				X	
Swab of Oral Mucosa[v]	X			X			X			X			X			X				X	
Swab of Herpetic Lesion for qPCR[w]			Within 3 days of occurrence of suspected lesion of herpetic origin																		
Blood for Anti-Pembrolizumab antibody[x]				X																	
Blood for Pembrolizumab PK[y]				X																	
RADIOGRAPHIC TUMOR/RESPONSE ASSESSMENTS																					
Radiographic (CT, PET/CT, or MRI) Scans & Tumor Assessment[z]	X									X									X	X	X
TREATMENT ADMINISTRATION																					
Talimogene Laherparepvec[ab]	X			X			X			X			X			X[ab]					
Pembrolizumab[ac]	X			X			X			X			X			X			X		
Post-treatment Observation[g,h]	X			X			X			X			X			X					
REPORTING EXPOSURE TO TALIMOGENE LAHERPAREPVEC																					
Exposure of Subject's Household member or Caregiver[ad]	→																				
Exposure of Subject's Healthcare Provider[ad]	→																				
[redacted]																					

Footnotes on the next page of the table

AE = adverse event; AFP = alpha fetoprotein; aPTT = activated partial thromboplastin time; CA 19-9 = cancer antigen 19-9; CEA = carcinoembryonic antigen; CRC = colorectal adenocarcinoma; CRF = case report form; CT = computed tomography; DRE = disease related event; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FT3 = free triiodothyronine; FT4 = free thyroxine; GEC = gastroesophageal cancer (adenocarcinoma or squamous cell carcinoma); HCC = hepatocellular carcinoma; HSV-1 = herpes simplex virus type 1; IgG = imunoglobulin G; INR = international normalization ratio; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; PET = positron emission tomography; PK = pharmacokinetics; PT = prothrombin time; PTT = partial thromboplastin time; qPCR = real-time polymerase chain reaction; SAE = serious adverse event; T3 = triiodothyronine; TSH = thyroid-stimulating hormone

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

[b] Procedures to be performed ≤ 10 days prior to enrollment.

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

[d] During treatment, assessments and procedures will be performed within ± 3 days of the planned visit, unless otherwise specified.

[e] Safety follow-up will be performed approximately 30 (+ 7) days after the last dose of talimogene laherparepvec.

[f] Subjects will be followed for survival by clinic visit or telephone contact approximately every 12 weeks ± 28 days from the date of the safety follow-up visit until up to approximately 24 months after the date of last subjects enrolled in Part 2 per tumor type. Subsequent anti-cancer treatments will be collected as part of the long-term follow-up survival assessment.

[g] Vital signs (blood pressure, resting heart rate, respiration rate, and temperature) must be performed prior to each talimogene laherparepvec administration.

[h] All subjects will undergo a 23 hour observation period following the first 3 cycles of talimogene laherparepvec treatment with vital signs (temperature, resting heart rate, systolic and diastolic blood pressure and respiratory rate) recorded every 30 minutes for the first 2 hours, hourly for the next 4 hours, then once every 4 to 6 hours with vital signs also obtained at the end of the observation period. For cycles 4 onwards, the observation period after each dose of talimogene laherparepvec may be reduced to a minimum of 6 hours at the investigator's discretion with vital signs recorded every 30 minutes for the first 2 hours and hourly for the next 4 hours and once at the end of the observational period. The subjects should be hospitalized if there is clinical deterioration during any observation period.

[i] All serious adverse events follow up to a serious adverse event, including death due to any cause that occur after the subject has signed the main informed consent through 90 (+7) days after the last administration of talimogene laherparepvec or pembrolizumab, 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 case report form. In addition, all serious adverse events that occur during the long-term safety follow-up period until the end of study are to be reported to Amgen and recorded in the CRF. As described in Section 9.2.3.2, there is no requirement to monitor study subjects for serious adverse events following the protocol required reporting period (as defined in Section 9.2.3) or after the end of study. However, these serious adverse events should be reported to Amgen (regardless of causality) if the investigator becomes aware of them (per regional regulatory requirements). All serious adverse events must be submitted to Amgen within 24 hours following the investigator's awareness of the event via the applicable CRF. All disease-related events and non-serious adverse events that occur, and concomitant medications that are administered after the first dose of talimogene laherparepvec or pembrolizumab through 30 (+7) days after the last administration of talimogene laherparepvec or pembrolizumab will be recorded in the events CRF.

[j] Only subsequent anti-tumor treatment will be recorded.

[k] During treatment blood samples for chemistry, hematology and coagulation panels will be collected weekly for the first 8 weeks of treatment and then prior to each talimogene laherparepvec administration until end of study treatment.

[l] Blood samples for thyroid function tests (triiodothyronine [T3] or free T3 [FT3] per local standard, free thyroxine [FT4], and thyroid-stimulating hormone [TSH]) will be collected at screening. Samples will be collected prior to study treatment administration on day 1 of weeks 1, 7, 13, 19, 25 and every 12 weeks thereafter until end of pembrolizumab treatment. Blood sample will also be collected at the safety follow-up visit. 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.

[m] Urine or serum pregnancy test to be performed on female of childbearing potential. Additional on-treatment pregnancy testing may be performed at the investigator's discretion or as defined in a county-specific protocol supplement at the end of the Appendix Section of the protocol as required per local laws and regulations.

[n] Disease specific assessments will only be performed on archived tissue (preferred) or screening biopsy tissue if results from previous testing are not available. Results should be submitted during screening and any time after enrollment. For details and a list of disease specific assessments refer to Section 7.2.1.

[o] During treatment blood samples for lactate dehydrogenase (LDH), carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP),and cancer antigen 19-9 (CA 19-9) will be collected at screening and at week 10 (± 1 week) and then every 9 weeks (± 1 week) prior to talimogene laherparepvec administration until end of study treatment.

[p] Hepatitis C and B panel should be performed at screening if serology has not been performed previously. Subjects who are positive for hepatitis B virus (HBV) and hepatitis C virus (HCV) infection should receive additional testing of viral load by polymerase chain reaction (PCR) and HCV genotype (if applicable) at screening and at the safety follow-up. For additional information refer to Section 7.2.1 through 7.2.3.1. In addition, HBSAg testing should be performed if ALT is elevated > 5x ULN and/or > 3 x baseline in subjects with hepatitis B. Refer to Table 15 for more details.

[q] Repeated Hepatitis B and/or C testing is only needed for Group B Cohort 6b

[redacted]

[t] During treatment blood and urine sample for real-time polymerase chain reaction (qPCR) testing of talimogene laherparepvec deoxyribonucleic acid (DNA) will be performed at the following time points: on Weeks 1 and 4 prior to talimogene laherparepvec administration and approximately 1 hour [± 15 minutes], 4 hours [± 30 minutes], 8 hours [± 1 hour], 24 [± 4] hours, 48 [± 4] hours, 7 days (± 2 days), and 14 days (± 2 days) following talimogene laherparepvec administration; on Week 7 prior to talimogene laherparepvec administration and 7 days (± 2 days) following talimogene laherparepvec administration; on Week 10 prior to talimogene laherparepvec administration; and at safety follow-up visit.

[u] Swabs of the surface of the injection sites and exterior of occlusive dressings for qPCR testing of talimogene laherparepvec DNA with or without 50% Tissue Culture Infective Dose (TCID50) assay of talimogene laherparepvec virus. During treatment the surface of the injection site will be swabbed at the following timepoints: on Weeks 1 and 4 prior to talimogene laherparepvec administration and 24 (± 4) hours, 48 (± 4) hours, 7 (± 2) days, and 14 (± 2) days following talimogene laherparepvec administration; on Week 7 prior to talimogene laherparepvec administration and 7 (± 2 days) following talimogene laherparepvec administration; and on Week 10 prior to talimogene laherparepvec administration. During treatment the exterior surface of the injection site dressings will be swabbed at the following timepoints: 24 (± 4) hours and 48 (± 4) hours after Week 1 and 4 talimogene laherparepvec administration and 7 (± 2) days after Week 1, 4, and 7 talimogene laherparepvec administrations.

[v] Swabs of oral mucosa: During treatment swabs of oral mucosa for qPCR testing of talimogene laherparepvec DNA with or without TCID50 assay for talimogene laherparepvec virus will be collected at the following visits: Week 1 and 4 prior to talimogene laherparepvec administration and 7 (± 2) days and 14 (± 2) days following talimogene laherparepvec administration; Week 7 prior to talimogene laherparepvec administration and 7 (± 2) days following talimogene laherparepvec administration; Week 10 and subsequent cycles prior to each talimogene laherparepvec administration. During safety follow-up, swabs of oral mucosa will be collected at the 30 (+7) day safety follow-up visit for qPCR testing of talimogene laherparepvec DNA.

[w] Swabs of any lesion suspected to be herpetic in origin (if any) will be collected during treatment and safety follow-up as follows: subject should 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 sent to the central laboratory for detection of talimogene laherparepvec DNA using qPCR testing.

[x] Blood for anti-pembrolizumab antibody (also termed immunogenicity) will be collected at day 1 of: cycle 1, cycle 2 , cycle 4, cycle 6, and cycle 8 of the additional treatment. All samples should be drawn within 24 hours before infusion of pembrolizumab and at the same time as predose trough blood collection for the PK sample.

[y] Blood for PK of pembrolizumab: Predose trough will be collected at day 1 of: cycle 1, cycle 2 , cycle 4, cycle 6, and cycle 8 of the additional treatment. All trough samples should be drawn within 24 hours before infusion of pembrolizumab.

[z] Radiographic tumor imaging: During treatment, radiographic tumor imaging will be performed independent of treatment cycle at week 10 (± 1 week) and then every 9 weeks (± 1 week) until confirmed progressive disease (PD) per modified immune-related response criteria (irRC) simulating RECIST version 1.1 (irRC-RECIST) (Appendix D). Radiographic imaging is required at the safety follow up visit if the subject ended treatment prior to documentation of confirmed PD per modified irRC-RECIST and has not had radiographic tumor imaging performed within 9 weeks (± 1 week) of the visit. Every effort should be made to complete radiographic assessments during the long-term follow-up approximately every 12 weeks (+ 1 week) until documented confirmed PD per modified irRC-RECIST, start of new anticancer treatment, death, or end of study, whichever occurs first, for subjects discontinuing study treatment for any reason other than confirmed PD. Response (complete response [CR], or partial response [PR]) or disease progression to be confirmed by second consecutive radiographic assessments no less than 4 weeks from the date of the first documented response or disease progression. Note: Confirmation of disease progression is required only in the absence of rapid clinical deterioration (ie, rapid decline in performance status) or symptomatic disease requiring rapid initiation of alternative systemic anti-cancer therapy.

[aa] To be performed if required by site for assessment of the intrahepatic lesion injection location. **As of Protocol Amendment 6 (dated 26 October 2021), intrahepatic injections of talimogene laherparepvec and liver biopsies are no longer performed in this study.**

[ab] If no progression is seen after a total of 6 cycles, up to 6 additional cycles of talimogene laherparepvec, at maximum tolerated dose if known or otherwise previously received dose, every 21 (± 3 days) may be administered, or the subject may proceed to alternative therapies depending on investigator discretion.

[ac] Pembrolizumab will be administered intravenously to subjects randomized at a dose of 200 mg every 3 weeks (± 3 days) starting at day 1 of week 1 until confirmed PD per modified irRC-RECIST (The same pattern of assessments continue if treatment exceeds week 18). Subjects can receive up to 35 cycles (approximately 24 months) with pembrolizumab.

[ad] Reporting potential or known unintended exposure to talimogene laherparepvec: 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 signs or symptoms suspected to be herpetic origin or is 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 DNA by qPCR testing in a swab taken from a lesion, if any, in a subject's household member, caregiver, or healthcare provider.

Table 12. Part 2 Schedule of Assessments for Talimogene Laherparepvec and Pembrolizumab Combination Treatment

Study Procedures	Screening			Study Treatment[d] (week/cycle number)																		Follow-up	
	≤ 28 days[a]	≤ 10 days[b]	≤ 72 hour[c]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	Safety[e]	Survival[f]
				Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6				
GENERAL ASSESSMENTS																							
Informed Consent	X																						
Review of Eligibility Criteria	X																						
Demographics	X																						
Medical and Surgical History	X																						
Vital Signs[g,h]	X			X			X			X			X			X			X			X	
Physical Exam	X			X																		X	
Weight	X			X			X			X			X			X			X			X	
ECOG Performance Status	X			X			X			X			X			X			X			X	
12-lead ECG	X																					X	
Child-Pugh Score	X																					X	
Recording of Concomitant Medication[i]	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→		X	X[j]
Review of DREs, AEs and SAEs[i]	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→		X	X
Survival Assessment																							X
LOCAL LABORATORY TESTS																							
Chemistry[k]		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	
Coagulation (PT/INR and PTT or aPTT)[k]		X		X	X	X	X	X	X	X			X			X			X			X	
Thyroid Function Tests (T3, FT3, FT4, TSH)[l]		X		X						X						X						X	
Urine or Serum Pregnancy Test[m]			X																			X	
Disease Specific Assessments[n]	X																						
Serum LDH[o]		X											X									X	
Hepatitis B and C Testing[p]		X								X[q]												X	
CEA (CRC Subjects Only)[o]		X											X									X	
AFP (HCC Subjects Only)[o]		X											X									X	

Footnotes and abbreviations after Table 13 below.

Table 12. Part 2 Schedule of Assessments for Talimogene Laherparepvec and Pembrolizumab Combination Treatment

Study Procedures	Screening			Study Treatment[d] (week/cycle number)																		Follow-up	
	≤ 28 days[a]	≤ 10 days[b]	≤ 72 hour[c]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	Safety[e]	Survival[f]
				Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6				
CENTRAL LABORATORY TESTS																							
HSV-1 IgG Antibody Serostatus				X						X												X	
[redacted]																							
Blood and Urine for qPCR[t]				X	X	X	X	X	X	X			X									X	
Swab of Injection Site Surfaces and Occlusive Dressings[u]				X	X	X	X	X	X	X													
Swab of Oral Mucosa[v]				X	X	X	X	X	X	X												X	
Swab of Herpetic Lesion for qPCR[w]				**Within 3 days of occurrence of suspected lesion of herpetic origin**																			
Radiographic (CT, PET/CT, or MRI) Scans & Tumor Assessment[x]	X												X									X	X
Optional liver ultrasound[y]		X																					
TREATMENT ADMINISTRATION																							
Talimogene Laherparepvec[z]				X			X			X			X			X			X				
Pembrolizumab[aa]				X			X			X			X			X			X				
Post-treatment Observation[h]				X			X			X			X			X			X				
REPORTING EXPOSURE TO TALIMOGENE LAHERPAREPVEC																							
Exposure of Subject's Household member or Caregiver[ab]				→																			
Exposure of Subject's Healthcare Provider[ab]				→																			
[redacted]																							

Footnotes and abbreviations after Table 13 below.

Table 13. Part 2 Schedule of Assessments for Talimogene Laherparepvec and Pembrolizumab Combination Treatment: Post Cycle 6

	Study Treatment[d] (week/cycle number)																			Follow-up	
Study Procedures	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	Pembrolizumab and Talimogene Laherparepvec Cycles 7-35	Safety[e]	Survival[f]
	Cycle 7			Cycle 8			Cycle 9			Cycle 10			Cycle 11			Cycle 12					
GENERAL ASSESSMENTS																					
Informed Consent																					
Review of Eligibility Criteria																					
Demographics																					
Medical and Surgical History																					
Vital Signs[g, h]	X			X			X			X			X			X			X	X	
Physical Exam	X																			X	
Weight	X			X			X			X			X			X			X	X	
ECOG Performance Status	X			X			X			X			X			X			X	X	
12-lead ECG																				X	
Child-Pugh Score																				X	
Recording of Concomitant Medication[i]	→																			X	X[j]
Review of DREs, AEs and SAEs[i]	→																			X	X
Survival Assessment																					X
LOCAL LABORATORY TESTS																					
Chemistry[k]	X			X			X			X			X			X			X	X	
Hematology[k]	X			X			X			X			X			X			X	X	
Coagulation (PT/INR and PTT or aPTT)[k]	X			X			X			X			X			X			X	X	
Thyroid Function Tests (T3, FT3, FT4, TSH)[l]	X						X													X	
Urine or Serum Pregnancy Test[m]																				X	
Serum LDH[o]	X									X										X	
Hepatitis B and C Testing[p]																				X	
CEA (CRC Subjects Only)[o]	X									X										X	
AFP (HCC Subjects Only)[o]	X									X										X	

Footnotes and abbreviations after Table 13 below.

Table 13. Part 2 Schedule of Assessments for Talimogene Laherparepvec and Pembrolizumab Combination Treatment: Post Cycle 6

	Study Treatment[d] (week/cycle number)																			Follow-up	
Study Procedures	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**Pembrolizumab and Talimogene Laherparepvec Cycles 7-35**	**Safety[e]**	**Survival[f]**
	Cycle 7			**Cycle 8**			**Cycle 9**			**Cycle 10**			**Cycle 11**			**Cycle 12**					
CENTRAL LABORATORY TESTS																					
HSV-1 IgG Antibody Serostatus																				X	
[redacted]																					
Blood and Urine for qPCR[t]																				X	
Swab of Oral Mucosa[v]																				X	
Swab of Herpetic Lesion for qPCR[w]			Within 3 days of occurrence of suspected lesion of herpetic origin																		
RADIOGRAPHIC TUMOR/RESPONSE ASSESSMENTS																					
Radiographic (CT, PET/CT, or MRI) Scans & Tumor Assessment[x]	X									X									X	X	X
TREATMENT ADMINISTRATION																					
Talimogene Laherparepvec[z]	X			X			X			X			X			X			X		
Pembrolizumab[aa]	X			X			X			X			X			X			X		
Post-treatment Observation[g,h]	X			X			X			X			X			X			X[ac]		
REPORTING EXPOSURE TO TALIMOGENE LAHERPAREPVEC																					
Exposure of Subject's Household member or Caregiver[ab]	→																				
Exposure of Subject's Healthcare Provider[ab]	→																				
[redacted]																					

Footnotes on the next page of the table

AE = adverse event; AFP = alpha fetoprotein; aPTT = activated partial thromboplastin time; CEA = carcinoembryonic antigen; CRC = colorectal adenocarcinoma; CRF = case report form; CT = computed tomography; DRE = disease related event; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FT3 = free triiodothyronine; FT4 = free thyroxine; HCC = hepatocellular carcinoma; HSV-1 = herpes simplex virus type 1; IgG = imunoglobulin G; INR = international normalization ratio; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; PET = positron emission tomography; PK = pharmacokinetics; PT = prothrombin time; PTT = partial thromboplastin time; qPCR = real-time polymerase chain reaction; SAE = serious adverse event; T3 = triiodothyronine; TSH = thyroid-stimulating hormone

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

[b] Procedures to be performed ≤ 10 days prior to enrollment.

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

[d] During treatment, assessments and procedures will be performed within ± 3 days of the planned visit, unless otherwise specified.

[e] Safety follow-up will be performed 30 (+ 7) days after the last dose of talimogene laherparepvec.

[f] Subjects will be followed for survival by clinic visit or telephone contact every 12 weeks ± 28 days from the date of the safety follow-up visit until up to approximately 24 months after the date of last subjects enrolled in Part 2 per tumor type. Subsequent anti-cancer treatments will be collected as part of the long-term follow-up survival assessment.

[g] Vital signs (blood pressure, resting heart rate, respiration rate, and temperature) must be performed prior to each talimogene laherparepvec administration.

[h] Subjects having intrahepatic injections will undergo a 6 hour observation period after each dose of talimogene laherparepvec with vital signs (temperature, resting heart rate, systolic and diastolic blood pressure and respiratory rate) recorded every 30 minutes for the first 2 hours and hourly for the next 4 hours and once at the end of the observation period. The subjects should be hospitalized if there is clinical deterioration during any observation period. Subjects who have cutaneous, subcutaneous, or nodal injections (no intrahepatic injections) must undergo a 1 hour observation period including vital signs at 30 minutes and 1 hour. **As of Protocol Amendment 6 (dated 26 October 2021), intrahepatic injections of talimogene laherparepvec and liver biopsies are no longer performed in this study.**

[i] All serious adverse events follow up to a serious adverse event, including death due to any cause that occur after the subject has signed the main informed consent through 90 (+7) days after the last administration of talimogene laherparepvec or pembrolizumab, 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 case report form. In addition, all serious adverse events that occur during the long-term safety follow-up period until the end of study are to be reported to Amgen and recorded in the CRF. As described in Section 9.2.3.2, there is no requirement to monitor study subjects for serious adverse events following the protocol required reporting period (as defined in Section 9.2.3) or after the end of study. However, these serious adverse events should be reported to Amgen (regardless of causality) if the investigator becomes aware of them (per regional regulatory requirements). All serious adverse events must be submitted to Amgen within 24 hours following the investigator's awareness of the event via the applicable CRF. All disease-related events and non-serious adverse events that occur, and concomitant medications that are administered after the first dose of talimogene laherparepvec or pembrolizumab through 30 (+7) days after the last administration of talimogene laherparepvec or pembrolizumab will be recorded in the events CRF.

[j] Only subsequent anti-tumor treatment will be recorded.

[k] During treatment blood samples for chemistry, hematology and coagulation panels will be collected weekly for the first 7 weeks of treatment and then prior to each talimogene laherparepvec administration until end of study treatment.

[l] Blood samples for thyroid function tests (triiodothyronine [T3] or free T3 [FT3] per local standard, free thyroxine [FT4], and thyroid-stimulating hormone [TSH]) will be collected at screening. Samples will be collected prior to study treatment administration on day 1 of weeks 1, 7, 13, 19, 25 and every 12 weeks thereafter until end of pembrolizumab treatment. Blood sample will also be collected at the safety follow-up visit. 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.

[m] Urine or serum pregnancy test to be performed on female of childbearing potential. Additional on-treatment pregnancy testing may be performed at the investigator's discretion or as defined in a county-specific protocol supplement at the end of the Appendix Section of the protocol as required per local laws and regulations.

[n] Disease specific assessments will only be performed on archived tissue (preferred) or screening biopsy tissue if results from previous testing are not available. Results should be submitted during screening and any time after enrollment. For details and a list of disease specific assessments refer to Section 7.2.1. For CRC subjects, if historical results are not available, the tests have to be completed locally. However, they do not need to be available at the time of enrollment.

[o] During treatment blood samples for lactate dehydrogenase (LDH), carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP) will be collected at screening and at week 10 (± 1 week) and then every 9 weeks (± 1 week) prior to talimogene laherparepvec administration until end of study treatment.

[p] If serology was negative and > 1 month ago the hepatitis panel should be repeated during screening. Subjects who are positive for hepatitis B virus (HBV) and hepatitis C virus (HCV) infection should receive additional testing of viral load by polymerase chain reaction (PCR) and HCV genotyping (if applicable) at screening, , and at the safety follow-up. For additional information refer to Section 7.2.1 through 7.2.3.1. In addition, HBSAg testing should be performed if ALT is elevated > 5 x ULN and/or > 3 x baseline in subjects with hepatitis B. Refer to Table 15 for more details.

[q] Repeated Hepatitis B and/or C testing is only needed for Arm VI (HCC with well-controlled hepatitis.

[redacted]

[t] During treatment blood and urine sample for real-time polymerase chain reaction (qPCR) testing of talimogene laherparepvec deoxyribonucleic acid (DNA) will be performed at the following time points: all subjects at weeks 1 and 4 will have samples taken prior to talimogene laherparepvec administration and 7 days (± 2 days) and 14 days (± 2 days) after talimogene laherparepvec administration and for subjects receiving intrahepatic injections additional samples will be taken at 1 hour [± 15 minutes]; following talimogene laherparepvec administration; on Week 7 prior to talimogene laherparepvec administration; on Week 10 prior to talimogene laherparepvec administration; and at safety follow-up visit. **As of Protocol Amendment 6 (dated 26 October 2021), intrahepatic injections of talimogene laherparepvec and liver biopsies are no longer performed in this study.**

[u] Swabs of the surface of the injection sites and exterior of occlusive dressings for qPCR testing of talimogene laherparepvec DNA with or without 50% Tissue Culture Infective Dose (TCID50) assay of talimogene laherparepvec virus. During treatment the surface of the injection site will be swabbed at the following timepoints: on Weeks 1 and 4 prior to talimogene laherparepvec administration 7 (± 2) days, and 14 (± 2) days following talimogene laherparepvec administration; on Week 7 prior to talimogene laherparepvec administration. During treatment the exterior surface of the injection site dressings will be swabbed at the following timepoints: 7 (± 2)days after Week 1 and 4 talimogene laherparepvec administrations.

[v] Swabs of oral mucosa: During treatment swabs of oral mucosa for qPCR testing of talimogene laherparepvec DNA with or without TCID50 assay for talimogene laherparepvec virus will be collected at the following visits: Week 1 and 4 prior to talimogene laherparepvec administration and 7 (± 2) days and 14 (± 2) days following talimogene laherparepvec administration; Week 7 prior to talimogene laherparepvec administration. During safety follow-up, swabs of oral mucosa will be collected at the 30 (+ 7) day safety follow-up visit for qPCR testing of talimogene laherparepvec DNA.

[w] Swabs of any lesion suspected to be herpetic in origin (if any) will be collected during treatment and safety follow-up as follows: subject should 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 sent to the central laboratory for detection of talimogene laherparepvec DNA using qPCR testing.

[x] Radiographic tumor imaging: During treatment, radiographic tumor imaging will be performed independent of treatment cycle at week 10 (± 1 week) and then every 9 weeks (± 1 week) until confirmed progressive disease (PD) per modified immune-related response criteria (irRC) simulating RECIST version 1.1 (irRC-RECIST) (Appendix D). Radiographic imaging is required at the safety follow up visit if the subject ended treatment prior to documentation of confirmed PD per modified irRC-RECIST and has not had radiographic tumor imaging performed within 9 weeks (± 1 week) of the visit. Every effort should be made to complete radiographic assessments during the long-term follow-up every 12 weeks (+ 1 week) until documented confirmed PD per modified irRC-RECIST, start of new anticancer treatment, death, or end of study, whichever occurs first, for subjects discontinuing study treatment for any reason other than confirmed PD. Response (complete response [CR], or partial response [PR]) or disease progression to be confirmed by second consecutive radiographic assessments no less than 4 weeks from the date of the first documented response or disease progression. Note: Confirmation of disease progression is required only in the absence of rapid clinical deterioration (ie, rapid decline in performance status) or symptomatic disease requiring rapid initiation of alternative systemic anti-cancer therapy.

[y] To be performed if required by site for assessment of the intrahepatic lesion injection location. **As of Protocol Amendment 6 (dated 26 October 2021), intrahepatic injections of talimogene laherparepvec and liver biopsies are no longer performed in this study.**

[z] If no progression is seen after a total of **12** cycles, a total of 35 cycles of talimogene laherparepvec, at maximum tolerated dose if known or otherwise previously received dose, every 21 (± 3 days) may be administered, or the subject may proceed to alternative therapies depending on investigator discretion. Dosing with talimogene laherparepvec beyond 12 cycles may be done if in the opinion of the investigator, the subject is deriving clinical benefit**.**

[aa] Pembrolizumab will be administered intravenously to subjects randomized at a dose of 200 mg every 3 weeks (± 3 days) starting at day 1 of week 1 until confirmed PD per modified irRC-RECIST (The same pattern of assessments continue if treatment exceeds week 18). Subjects can receive up to 35 cycles (approximately 24 months) with pembrolizumab.

[ab] Reporting potential or known unintended exposure to talimogene laherparepvec: 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 signs or symptoms suspected to be herpetic origin or is 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 DNA by qPCR testing in a swab taken from a lesion, if any, in a subject's household member, caregiver, or healthcare provider.

[ac] Post treatment observation will only be needed after cycle 12 where talimogene laherparepvec is being injected into liver.

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, unless otherwise indicated. 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 unless otherwise noted.

Copies of imaging studies may be collected and held at an independent centralized radiology vendor for potential retrospective evaluation.

The following laboratory analytes in Table 14 will be assessed at various times throughout the study:

Table 14. Laboratory Analytes

Chemistry	Hematology	Biodistribution and Shedding	Biomarker	Other Labs
Sodium Potassium Chloride Total protein Albumin Calcium Creatinine BUN Glucose TBL Alkaline-phosphatase AST ALT	RBC Hemoglobin Hematocrit Platelets WBC Differential[a] • Neutrophils • Eosinophils • Basophils • Lymphocytes • Monocytes	qPCR for talimogene laherparepvec DNA $TCID_{50}$ assay for talimogene laherparepvec virus	HSV-1 IgG antibody [redacted]	Pregnancy HBV and HCV testing LDH CEA (CRC, GEC adenocarcinoma only) AFP (HCC only) Part 1 only: CA 19-9 (GEC, CRC, HCC only) Coagulation (PT, INR, PTT, aPTT)
Pembrolizumab related labs: Thyroid function tests (T3, FT3, FT4, TSH) Part 1 only: Blood for anti-pembrolizumab antibody Blood for pembrolizumab PK				Biopsy Labs KRAS exon 2, RAS (KRAS non exon 2, NRAS), BRAF (CRC only) ALK, ROS1 (NSCL only) HER2-neu IHC ± FISH (GEC only) Estrogen receptor, progesterone receptor, HER2-neu (BC) BRAF for melanoma [redacted]

AFP = alpha-fetoprotein; ALK = anaplastic lymphoma kinase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BC = breast adenocarcinoma; BCC = basal cell carcinoma, BRAF = v-raf murine sarcoma viral oncogene homolog B; BUN = blood urea nitrogen; CA 19-9 = cancer antigen 19-9; [redacted]
CEA = carcinoembryonic antigen; CRC = colorectal adenocarcinoma; FISH = fluorescence in situ hybridization; FT3 = free triiodothyronine; FT4 = free thyroxine; GEC gastroesophageal adenocarcinoma; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HER2 = human epidermal growth factor receptor 2; HSV-1 = herpes simplex virus; [redacted]
IgG = immunoglobulin G; IHC = immunohistochemistry; INR = international normalized ratio; KRAS = Kristen rat sarcoma viral oncogene homolog; LDH = lactate dehydrogenase; NRAS = neuroblastoma retrovirus-associated DNA sequences (RAS); NSCL = non-small cell lung; PD-L1 = programmed cell death ligand 1; PK = pharmacokinetic; PT = prothrombin time; PTT = partial thromboplastin time; qPCR = real-time polymerase chain reaction; RBC = red blood cell count; ROS1 = proto-oncogene receptor tyrosine kinase; T3 = triiodothyronine; TBL = total bilirubin; $TCID_{50}$ = 50% tissue culture infectious dose; TSH = thyroid-stimulating hormone; WBC = white blood cell count
[a] 3-part differential if 5-part unable to be performed.

All tests ([redacted]) are to be performed at a local laboratory and to be fully and routinely recorded on eCRFs. Chemistry, hematology and coagulation panels performed during treatment will be collected prior to each talimogene laherparepvec and/or pembrolizumab administration until the end of study treatment. Missed tests that are not done must be reported as such on the CRFs. [redacted]

Procedures deemed necessary as part of standard of care or as required by local laws and regulations may be performed at the Investigator's discretion.

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

7.2.1 Screening and Enrollment

The following procedures are to be completed during the screening period within 28 days of enrollment (unless otherwise noted) at time points designated in the Schedule of Assessments (Table 8 and Table 10, Section 7.1):

Within ≤ 28 days prior to enrollment:

- Confirmation that the ICF has been signed
- Registration of screening in IVR system (refer to Section 5).
- Review eligibility criteria
- Demographic Data: Gender, age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness.
- Medical and Surgical History: The Investigator or designee will collect complete medical and surgical history. Medical history will include information on the subject's concurrent medical conditions. Record all findings on the medical history CRF.
- Vital Signs: Systolic/diastolic blood pressure, resting heart rate, respiratory rate and temperature must be performed prior to enrollment. Subject is preferred to 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. The temperature location selected for a subject should be the same that is used throughout the study and documented on the vital signs CRF.
- Physical Examination: Performed as per standard of care.
- Weight in kilogram should be measured without shoes
- ECOG performance status assessment

- 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.
- Child-Pugh Score (Appendix F)
- Recording of Concomitant Medications: Concomitant medications that are administered after the subject has signed the main ICF through 30 (+7) days after the last administration of talimogene laherparepvec will be recorded in the concomitant medications CRF.
- Review of Serious Adverse Events: All serious adverse events, follow-up to a serious adverse event, including death due to any cause that occur after the subject has signed the main ICF through 90 (+7) days after last administration of talimogene laherparepvec and/or pembrolizumab, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier will be reported to Amgen, within 24 hours of the investigator's awareness of the event, and recorded in the events CRF.
- Liver Tumor Biopsy (Part 1) or Tumor Biopsy (Part 2): Screening biopsy should only be performed for those subjects who have no prior biopsy to confirm that their disease is one of the eligible tumor types. Those that have had prior pathology reports supporting their diagnosis do not need screening biopsy.
- Radiographic Tumor Assessment: radiographic tumor imaging (CT, positron emission tomography [PET]/CT with contrast, and/or MRI with contrast) encompassing the chest, abdomen, pelvis and all other sites of disease will be performed at screening and will be used as baseline. If intrahepatic injections are planned, a liver MRI with contrast or multiphase CT of the liver must also be performed at screening. A brain MRI or CT with contrast must be performed for subjects with NSCLC or melanoma and all subjects that have had a history of cerebral metastases. Any of the above radiographic tumor assessments that are part of routine care but were completed prior to informed consent may be used if still within the required window.
- Disease Specific Assessments: If no historical results are available from standard of care assessments, the disease specific assessments can be performed on archived tissue by central laboratory. Results should be submitted during screening and any time after enrollment. Assessments will include the following:

BCC subjects: PTCH mutation status if known will also be collected but is not mandatory.

CRC subjects:

Kristen rat sarcoma viral oncogene homolog (KRAS) exon 2 gene status,

Extended RAS testing (KRAS non-exon 2 and neuroblastoma RAS viral oncogene homolog (NRAS) gene status) only if KRAS exon 2 gene is wild type

B-Raf sarcoma viral oncogene homolog (BRAF) gene status

microsatellite instability or mismatch repair.

CRC subjects (Part 2 only):

If historical results are not available, the above tests have to be completed locally. However, they do not need to be available at the time of enrollment.

GEC subjects: HER2-neu immunohistochemistry (IHC) ± fluorescent in situ hybridization (FISH).

Melanoma subjects: BRAF gene status.

NSCLC non-squamous cell subjects: anaplastic lymphoma kinase (ALK) and EGFR mutation testing. ROS1 mutation status if known will also be collected but is not mandatory.

BC subjects: estrogen receptor, progesterone receptor, and HER2-neu testing. Breast cancer susceptibility gene 1 and 2 (BRCA 1 and 2) mutation status if known will also be collected but is not mandatory

Within ≤ 10 days prior to enrollment by local laboratory:

- Chemistry Panel: sodium, potassium, chloride, total protein, albumin, calcium, creatinine, BUN, glucose, TBL, ALP, AST, ALT
- Hematology Panel: RBC count, hemoglobin, hematocrit, platelets, white blood cell (WBC) count with 5-part differential (3-part differential if 5-part unable to be performed): neutrophils, eosinophils, basophils, lymphocytes, monocytes
- Coagulation (PT or INR and PTT or aPTT)
- Combination treatment only (Part 1 Cohorts 5 & 6 and Part 2): Thyroid Function Tests (triiodothyronine [T3] or free triiodothyronine [FT3], free thyroxine [FT4] and thyroid-stimulating hormone [TSH])

  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
- Serum lactate dehydrogenase (LDH)
- Carcinoembryonic antigen (CEA) (CRC and GEC adenocarcinoma subjects only)
- Alpha fetoprotein (AFP) (HCC subjects only)
- Cancer antigen 19-9 (CA 19-9; Part 1 only) (GEC, CRC and HCC subjects only)
- Determination of Hepatitis B and C Status:

If Hepatitis B status is known to be positive by serology and subject is candidate for Group B, additional testing for HBV DNA by polymerase chain reaction (PCR) is necessary.

If Hepatitis C status is known to be positive by serology, additional testing for HCV DNA by PCR and genotyping (if not previously done) is necessary

If Hepatitis B and/or Hepatitis C status is not known to be positive by serology, the following laboratory testing is required:

Hepatitis B Surface Antigen (HepBsAg) and total Hepatitis B Core Antibody (HepBcAb):

- If results are HepBcAb positive and HepBsAg negative, additional testing for HBV DNA by PCR is necessary

HCV antibody:

- If results are HCV antibody positive, additional testing for HCV RNA by PCR and HCV genotyping is necessary.

Within ≤ 10 days prior to enrollment by local imaging (Optional test):

- Liver ultrasound is not required during screening but may be done by site for intrahepatic injection evaluation and planning

Within ≤ 72 hours prior to enrollment:

- Serum or urine pregnancy test for female subjects of childbearing potential. Additional on-treatment pregnancy testing may be performed at the investigator's discretion or as defined in a country-specific supplement at the end of the Appendix Section of the protocol as required per local laws and regulations.

Subjects who are determined not eligible after screening must be screen-failed in the IVR system 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 consent form is signed within 28 days of enrollment. Subjects who are determined not eligible after rescreen must be screen-failed in the IVR system and the reason for the screen-failure provided. Subjects may only be enrolled once into this study.

7.2.2 Treatment

As of Protocol Amendment 6 (dated 26 October 2021), intrahepatic injections of talimogene laherparepvec and liver biopsies are no longer performed in this study.

Treatment begins when the first dose of talimogene laherparepvec alone or in combination with pembrolizumab is administered to a subject. If possible, talimogene laherparepvec should be administered before pembrolizumab. Study treatment should begin as soon as possible after registering enrollment of the subject via IVRS but no later than 5 days after enrollment. Study treatment is to be administered after all other procedures are completed during each visit unless otherwise stated.

Observation Period for Subjects Enrolled into Part 1:

Subjects must be monitored in the hospital for 23 hours after each injection for the first 3 cycles of talimogene laherparepvec before discharge to home. The observation period may be reduced, at the investigator's discretion, to a minimum of 6 hours after each injection for cycles 4 onwards. Monitoring should continue if there are any signs of clinical deterioration.

Observation Period for Subjects Enrolled into Part 2:

As of Protocol Amendment 6 (dated 26 October 2021), intrahepatic injections of talimogene laherparepvec and liver biopsies are no longer performed in this study.

Subjects receiving intrahepatic injections must be monitored in the hospital for a minimum of 6 hours after injection of talimogene laherparepvec before discharge home. The monitoring should continue if there are any signs of clinical deterioration and at the investigator's discretion.

Subjects who do not receive an intrahepatic injection (ie., only nodal, cutaneous, or subcutaneous) must be monitored for 1 hour following the talimogene laherparepvec injections.

The following procedures will be completed during the treatment period at the times designated in the Schedule of Assessments (Table 8 through Table 13, Section 7.1). During treatment, assessments and procedures will be performed within ± 3 days of the planned visit, unless otherwise specified.

- Vital Signs: Systolic/diastolic blood pressure, resting heart rate, respiratory rate, and temperature must be performed prior to each talimogene laherparepvec administration and during the observation period (if applicable) following each dose. During the observation period vital signs must be recorded:
  - every 30 minutes for the first 2 hours (every 30 minutes for 1 hour for subjects who do not have an intrahepatic injection)
  - hourly for the next 4 hours
  - once every 4 to 6 hours until the end of the observation period, where applicable
  - once at the end of the observation period
- Subject is preferred to 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 signs CRF. Record all measurements on the vital signs CRF. The temperature location selected for a subject should be the same that is used throughout the study and documented on the vital signs CRF.
- Physical Examination: Performed as per standard of care (week 1 only)
- Weight in kilogram should be measured without shoes prior to each talimogene laherparepvec administration
- ECOG Performance Status prior to each talimogene laherparepvec administration
- Local laboratory tests: Screening laboratory values may be used for day 1 week 1 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 scheduled dose of study drug.

Chemistry Panel: sodium, potassium, chloride, total protein, albumin, calcium, creatinine, BUN, glucose, TBL, ALP, AST, ALT. In Part 1, chemistry panel will be performed weekly for the first 8 weeks of treatment and then prior to each study drug administration until end of study treatment. In Part 2, chemistry panel will be performed weekly for the first 7 weeks of treatment and then prior to each study drug administration until end of study treatment.

Hematology Panel: RBC count, hemoglobin, hematocrit, platelets, WBC count with 5-part differential (3-part differential if 5-part unable to be performed): neutrophils, eosinophils, basophils, lymphocytes, monocytes. In Part 2, hematology panel will be performed weekly for the first 7 weeks of treatment and then prior to each study drug administration until end of study treatment.

In Part 1, coagulation (PT or INR and PTT or aPTT) will be performed weekly for the first 8 weeks of treatment and then prior to each study drug administration until end of study treatment. In Part 2, coagulation will be performed weekly for the first 7 weeks of treatment and then prior to each study drug administration until end of study treatment.

Serum LDH at week 10 and then every 9 (± 1) weeks until end of treatment prior to study drug administration

CEA (CRC and GEC adenocarcinoma subjects only) at week 10 and then every 9 (± 1) weeks until end of treatment prior to study drug administration

AFP (HCC subjects only) at week 10 and then every 9 (± 1) weeks until end of treatment prior to study drug administration

CA 19-9 (GEC, CRC and HCC subjects only) at week 10 and then every 9 (± 1) weeks until end of treatment prior to study drug administration

For HCC subjects with well-controlled hepatitis (Part 1 Group B, Cohort 6b and Part 2 Arm VI with well-controlled hepatitis): HBV DNA by PCR and HCV RNA by RT-PCR at week 7 and as clinically indicated

- Specialized / Central Laboratory Tests at the following timepoints during study treatment:

Blood for HSV-1 IgG Antibody Serostatus: prior to talimogene laherparepvec administration at weeks 1 and 7

[redacted]

In Part 1, blood for anti-pembrolizumab antibody (immunogenicity):

- Day 1 of: cycle 1, cycle 2 , cycle 4, cycle 6, and cycle 8 of the additional treatment.
- Note: All samples should be drawn within 24 hours before infusion of pembrolizumab and at the same time as the predose trough blood collection for the PK sample.

In Part 1, blood for PK of pembrolizumab:

- Predose trough will be collected at day 1 of: cycle 1, cycle 2 , cycle 4, cycle 6, and cycle 8 of the additional treatment.
- Note: All trough samples should be drawn within 24 hours before infusion of pembrolizumab.

Liver Tumor Biopsy/Tumor biopsies **(As of Protocol Amendment 6 [dated 26 October 2021], liver biopsies are no longer performed in this study)**: Liver tumor biopsies (Part 1) or tumor biopsies (Part 2) will be performed immediately prior to the talimogene laherparepvec administration at weeks 1, 7 and 16. Screening biopsy may be used for baseline (week 1) biopsy if subject is eligible, provided enough tissue has been obtained. Biopsies will be taken at the following timepoints:

- Week 1 – biopsy a lesion planned for injection
- Week 7 – biopsy a lesion planned for injection and/or a lesion you have already injected and plan to inject again
- Week 16 – biopsy a lesion planned for injection and/or a lesion you plan to inject again

Refer to Laboratory Manual for further detail on tumor biopsy procedures.

Blood and Urine for qPCR Testing of Talimogene Laherparepvec DNA:

Part 1

- Week 1 prior to talimogene laherparepvec administration and approximately 1 hour (± 15 minutes), 4 hours (± 30 minutes), 8 hours (± 1 hour), 24 hours (± 4 hours), 48 hours (± 4 hours), 7 (± 2) days and 14 (± 2) days) after talimogene laherparepvec administration
- Week 4 prior to talimogene laherparepvec administration and approximately 1 hour (± 15 minutes), 4 hours (± 30 minutes), 8 hours (± 1 hour), 24 hours (± 4 hours), 48 hours (± 4 hours), 7 (± 2) days, and 14 (± 2) days after talimogene laherparepvec administration
- Week 7 prior to talimogene laherparepvec administration and 7 (± 2) days after talimogene laherparepvec administration
- Week 10 prior to talimogene laherparepvec administration

Part 2

- Week 1 prior to talimogene laherparepvec administration and:
  - For subjects receiving intrahepatic injections; 1 hour (± 15 minutes)
  - For all subjects 7 (± 2) days and 14 (± 2) days) after talimogene laherparepvec administration
- Week 4 prior to talimogene laherparepvec administration and
  - For subjects receiving intrahepatic injections 1 hour (± 15 minutes)
  - For all subjects 7 (± 2) days, and 14 (± 2) days after talimogene laherparepvec administration
- Week 7 prior to talimogene laherparepvec administration and
- Week 10 prior to talimogene laherparepvec administration.

Swabs of Surface of Injection Site for qPCR Testing with or without 50% Tissue Culture Infective Dose (TCID50) Assay: during treatment swabs of the surface of the injection site for qPCR testing of talimogene laherparepvec DNA Swabs of the surface of the injection site for qPCR testing of talimogene laherparepvec DNA and if qPCR testing is positive, then a TCID50 assay will be performed to evaluate whether the talimogene laherparepvec virus is detectable in the sample:

Part 1

- Week 1 prior to talimogene laherparepvec administration and 24 hours (± 4 hours), 48 hours (± 4 hours), 7 (± 2) days and 14 (± 2) days after talimogene laherparepvec administration
- Week 4 prior to talimogene laherparepvec administration and 24 hours (± 4 hours), 48 hours (± 4 hours), 7 (± 2) days, 14 (± 2) days after talimogene laherparepvec administration
- Week 7 prior to talimogene laherparepvec administration and 7 (± 2) days after talimogene laherparepvec administration,
- Week 10 prior to talimogene laherparepvec administration.

Part 2

- Week 1 prior to talimogene laherparepvec administration and 7 (± 2) days and 14 (± 2) days after talimogene laherparepvec administration
- Week 4 prior to talimogene laherparepvec administration and 7 (± 2) days, 14 (± 2) days after talimogene laherparepvec administration
- Week 7 prior to talimogene laherparepvec administration.

Swabs of Exterior Surface of Injection Site Dressing for qPCR Testing with or without TCID50 Assay: during treatment swabs of the exterior surface of injection site dressing for qPCR testing of talimogene laherparepvec DNA and if qPCR testing is positive, then a TCID50 assay will be performed to evaluate whether the talimogene laherparepvec virus is detectable in the sample:

Part 1

- Week 1: 24 hours (± 4 hours), 48 hours (± 4 hours), 7 (± 2) days after talimogene laherparepvec administration

- Week 4: 24 hours (± 4 hours), 48 hours(± 4 hours), 7 (± 2) days after talimogene laherparepvec administration
- Week 7: 7 (± 2) days after talimogene laherparepvec administration.

Part 2

- Week 1: 7 (± 2) days after talimogene laherparepvec administration
- Week 4: 7 (± 2) days after talimogene laherparepvec administration

Swabs of Oral Mucosa for qPCR Testing with or without TCID50 Assay: during treatment swabs of oral mucosa for qPCR testing of talimogene laherparepvec DNA and if qPCR testing is positive, then a TCID50 assay will be performed to evaluate whether the talimogene laherparepvec virus is detectable in the sample:

Part 1

- Week 1 prior to talimogene laherparepvec administration and 7 (± 2) days and 14 (± 2) days after talimogene laherparepvec administration
- Week 4 prior to talimogene laherparepvec administration and 7 (± 2) days and 14 (± 2) days after talimogene laherparepvec administration
- Week 7 prior to talimogene laherparepvec administration and 7 (± 2 days) after talimogene laherparepvec administration
- Week 10 and subsequent cycles prior to talimogene laherparepvec administration.

Part 2

- Week 1 prior to talimogene laherparepvec administration and 7 (± 2) days and 14 (± 2) days after talimogene laherparepvec administration
- Week 4 prior to talimogene laherparepvec administration and 7 (± 2) days and 14 (± 2) days after talimogene laherparepvec administration
- Week 7 prior to talimogene laherparepvec administration.

Swabs of Herpetic Lesions for qPCR Testing of Talimogene Laherparepvec DNA: Swab of any lesions suspected to be herpetic in origin (if any) will be collected as follows: subject should return to clinic within 3 days of the occurrence of reportable lesion suspected to be herpetic in origin such as cold sore or vesicles. Lesions should be evaluated and swabbed if HSV infection is suspected. Sample should be sent to the central laboratory for detection of talimogene laherparepvec DNA using qPCR testing.

- Radiographic Tumor Assessment (Week 10 and every 9 weeks thereafter): During treatment, radiographic tumor imaging of the chest, abdomen, and pelvis and any other sites of known disease will be performed independent of treatment cycle at week 10 (± 1 week) and then every 9 weeks (± 1 week) until confirmed PD per modified irRC-RECIST. Radiographic imaging is required at the safety follow up visit if the subject ended treatment prior to clinically relevant disease progression and has not had radiographic tumor imaging performed within 9 weeks (± 1 week) of the visit. In Part 2, clinical tumor assessment should be documented as well, if applicable. Every effort should be made to complete radiographic assessments during the long-term follow-up until documentation of confirmed PD per modified irRC-RECIST for subjects discontinuing treatment for any reason other than PD. Response (CR, or PR) or disease progression to be confirmed by second consecutive radiographic assessments no less than 4 weeks from the date of the first documented response or disease progression. Note: Confirmation of disease progression is required only in

the absence of rapid clinical deterioration (ie, rapid decline in performance status) or symptomatic disease requiring rapid initiation of alternative systemic anti-cancer therapy).

- Talimogene laherparepvec administration (Q21D [+ 3 days] for cycle 1, and Q21D [± 3 days] for all subsequent cycles) with observation period as applicable.
    - Part 1 – Maximum of 12 cycles of talimogene laherparepvec will be administered
    - Part 2 – Maximum of 35 cycles of talimogene laherparepvec will be administered
- Clinical tumor assessments for talimogene laherparepvec administration 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.
- Pembrolizumab administration
    - Day 1 of weeks 1, 4, 7, 10, 13, 16, and Q3W (± 3 days) thereafter until end of study treatment
    - Subjects can receive up to 35 cycles (approximately 24 months) with pembrolizumab
- Recording of Concomitant Medications: Concomitant medications should be assessed on an ongoing basis and recorded in the concomitant CRF at each subject visit.
- Review of Disease Related Events: Disease related adverse events should be assessed on an ongoing basis. All disease adverse events that occur after the first dose of talimogene laherparepvec or pembrolizumab through 30 (+7) days after the last administration of talimogene laherparepvec or pembrolizumab, whichever is later, will be recorded in the events CRF. All serious disease-related events will be recorded and reported to the sponsor or designee within 24 hours of the investigator's awareness of the event.
- Review of Adverse Events and Serious Adverse Events: Adverse events should be assessed on an ongoing basis. All non-serious treatment-emergent adverse events that occur after the first dose of talimogene laherparepvec or pembrolizumab through 30 (+7) days after the last administration of talimogene laherparepvec or pembrolizumab, whichever is later, will be recorded in the events CRF.
  All serious adverse events that occur after the subject has signed the main informed consent through 90 (+7) days after the last administration of talimogene laherparepvec or pembrolizumab, or 30 days following cessation of study drugs if the subjects initiates new anticancer therapy, whichever is earlier), will be reported to Amgen, within 24 hours of the investigator's awareness of the event, and recorded in the events CRF.
- Report 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]

7.2.3 Long-term Follow-up

7.2.3.1 Safety Follow-up

Upon permanent discontinuation from the study treatment for any reason, the following procedures will be performed 30 (+7) days after the last dose of talimogene laherparepvec for the monotherapy cohorts (Cohorts 1, 2, 3 and 4 in Part 1), or 30 (+ 7) days after the last dose of talimogene laherparepvec or pembrolizumab, whichever is later, for the combination treatment (Cohorts 5 and 6 in Part 1, and all arms in Part 2).

- Vital signs (systolic/diastolic blood pressure, resting heart rate, respiratory 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 documented on the vital sign CRF. Record all measurements on the vital signs CRF. The temperature location selected for a subject should be the same that is used throughout the study and documented on the vital signs CRF.
- Physical examination as per standard of care
- Weight in kilogram should be measured without shoes
- ECOG performance status assessment
- 12-lead 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.
- Recording of Concomitant Medications: All concomitant medications that are administered after the subject has signed the main informed consent through 30 (+7) days after the last administration of talimogene laherparepvec will be recorded in the concomitant medications CRF.
- Review of Disease Related Events: Disease related adverse events should be assessed on an ongoing basis. All disease adverse events that occur after the first dose of talimogene laherparepvec or pembrolizumab through 30 (+7) days after the last administration of talimogene laherparepvec or pembrolizumab, whichever is later, will be recorded in the events CRF. All serious disease-related events will be recorded and reported to the sponsor or designee within 24 hours of the investigator's awareness of the event.

- Review of Adverse events and Serious Adverse Events: Adverse events should be assessed on an ongoing basis. All nonserious adverse events that occur after the first dose of talimogene laherparepvec or pembrolizumab through 30 (+7) days after the last administration of talimogene laherparepvec or pembrolizumab, whichever is later, will be recorded in the events CRF.
  All serious adverse events that occur after the subject has signed the main informed consent through 90 (+7) days after the last administration of talimogene laherparepvec, or pembrolizumab, or 30 days following cessation of study drugs if the subject initiates new anticancer therapy, whichever is earlier), will be reported to Amgen and recorded in the events CRF. In addition, all serious adverse events that occur during the long-term safety follow-up period until the end of study are to be reported to Amgen and recorded in the CRF. As described in Section 9.2.3.2, there is no requirement to monitor study subjects for serious adverse events following the protocol required reporting period (as defined in Section 9.2.3) or after the end of study. However, these serious adverse events should be reported to Amgen (regardless of causality) if the investigator becomes aware of them (per regional regulatory requirements). All serious adverse events must be submitted to Amgen within 24 hours following the investigator's awareness of the event via the applicable CRF.
- Child-Pugh score
- Local laboratory tests:
  - Chemistry panel: sodium, potassium, chloride, total protein, albumin, calcium, creatinine, BUN, glucose, TBL, ALP, AST, ALT
  - Hematology panel: RBC count, hemoglobin, hematocrit, platelets, WBC count with 5-part differential (3-part differential if 5-part unable to be performed): neutrophils, eosinophils, basophils, lymphocytes, monocytes
  - Coagulation (PT or INR and PTT or aPTT)
  - Serum LDH
  - For subjects with chronic HBV and HCV infection repeat testing for HBV DNA by PCR or HCV RNA by PCR, respectively
- Local laboratory, if available, or central laboratory:
  - CEA (CRC and GEC adenocarcinoma subjects only)
  - AFP (HCC subjects only)
  - CA 19-9 (Part 1 only GEC, CRC and HCC subjects only)
  - Serum or urine pregnancy test for female subjects of childbearing potential
- Specialized / Central Laboratory Tests
  - HSV-1 IgG Antibody Serostatus
  - [redacted]
  - Blood and Urine for qPCR Testing of Talimogene Laherparepvec DNA
  - Swab of Oral Mucosa
  - Swab of Herpetic Lesion for qPCR Testing of Talimogene Laherparepvec DNA
- Radiographic Tumor Assessment: During treatment, radiographic tumor imaging will be performed independent of treatment cycle at week 10 (± 1 week) and then every 9 weeks (± 1 week) until confirmed PD per modified irRC simulating RECIST version 1.1 (irRC-RECIST) (Appendix D). Radiographic imaging is required at the safety follow-up visit if the subject ended treatment prior to documentation of confirmed PD and has not had radiographic tumor imaging performed within 9 weeks (± 1 week) of the visit. Every effort should be made to complete radiographic

assessments during the long-term follow-up approximately every 12 weeks (+ 1 week) until documented confirmed PD per modified irRC-RECIST, start of new anticancer treatment, death, or end of study, whichever occurs first, for subjects discontinuing treatment for any reason other than confirmed PD. In Part 2, clinical tumor assessment, if applicable, should be performed and documented at these timepoints as well. Response (CR, or PR) or PD to be confirmed by second consecutive radiographic assessments no less than 4 weeks from the date of the first documented response or PD.

- Report 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.

7.2.3.2 Survival Follow-up

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, talimogene laherparepvec-related adverse events, and initiation of additional anti-tumor treatment. For subjects in the combination treatment cohort, the long-term follow-up starts after the discontinuation of whichever study drug is discontinued last.

For Part 1, contact for all subjects will be attempted approximately every 12 weeks (± 28 days) following the safety follow-up visit until death, subject withdrawal, or up to approximately 24 months after the date of the last subject enrolled in Part 1. Subjects in Cohort 5 and 6 will be followed approximately 24 months after the last subject enrolled in their cohort in Part 1, or approximately 24 months after the last subject enrolled with their tumor type in Part 2, whichever is later.

For Part 2, contact for all subjects will be attempted approximately every 12 weeks (± 28 days) following the safety follow-up visit until death, subject withdrawal, or up to approximately 24 months after the date of the last subject enrolled in that tumor cohort.

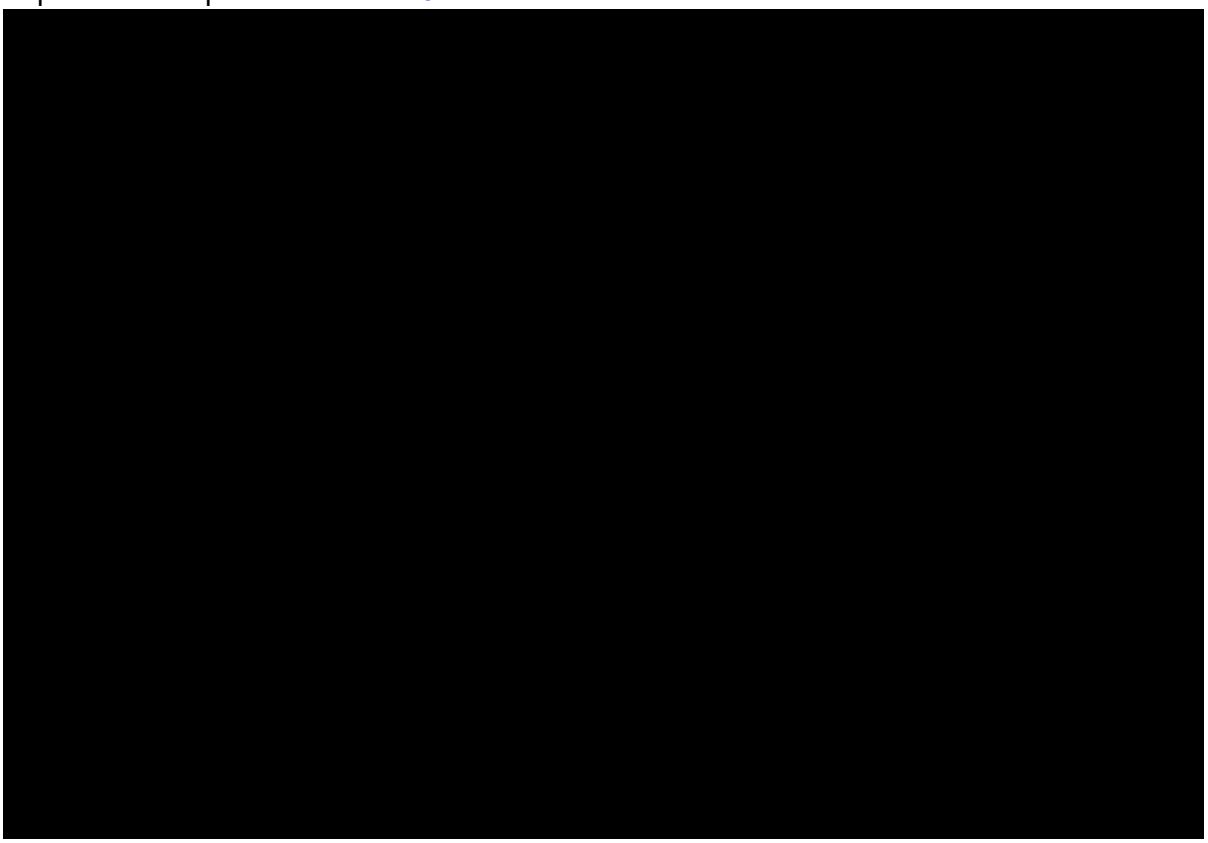
Radiographic Tumor Assessment: Every effort should be made to complete radiographic assessments approximately every 12 (+1) weeks during the long-term follow-up until documentation of PD per modified irRC-RECIST (Appendix D), start of new anticancer treatment, death, or end of study, whichever occurs first, for subjects discontinuing treatment for any reason other than PD. In Part 2, clinical tumor assessment, if applicable, should be performed and documented at these timepoints as well. Response (CR, or PR) or disease progression to be confirmed by second consecutive radiographic assessments no less than 4 weeks from the date of the first documented response or disease progression. Note: Confirmation of disease progression is required only in the absence of rapid clinical deterioration (ie, rapid

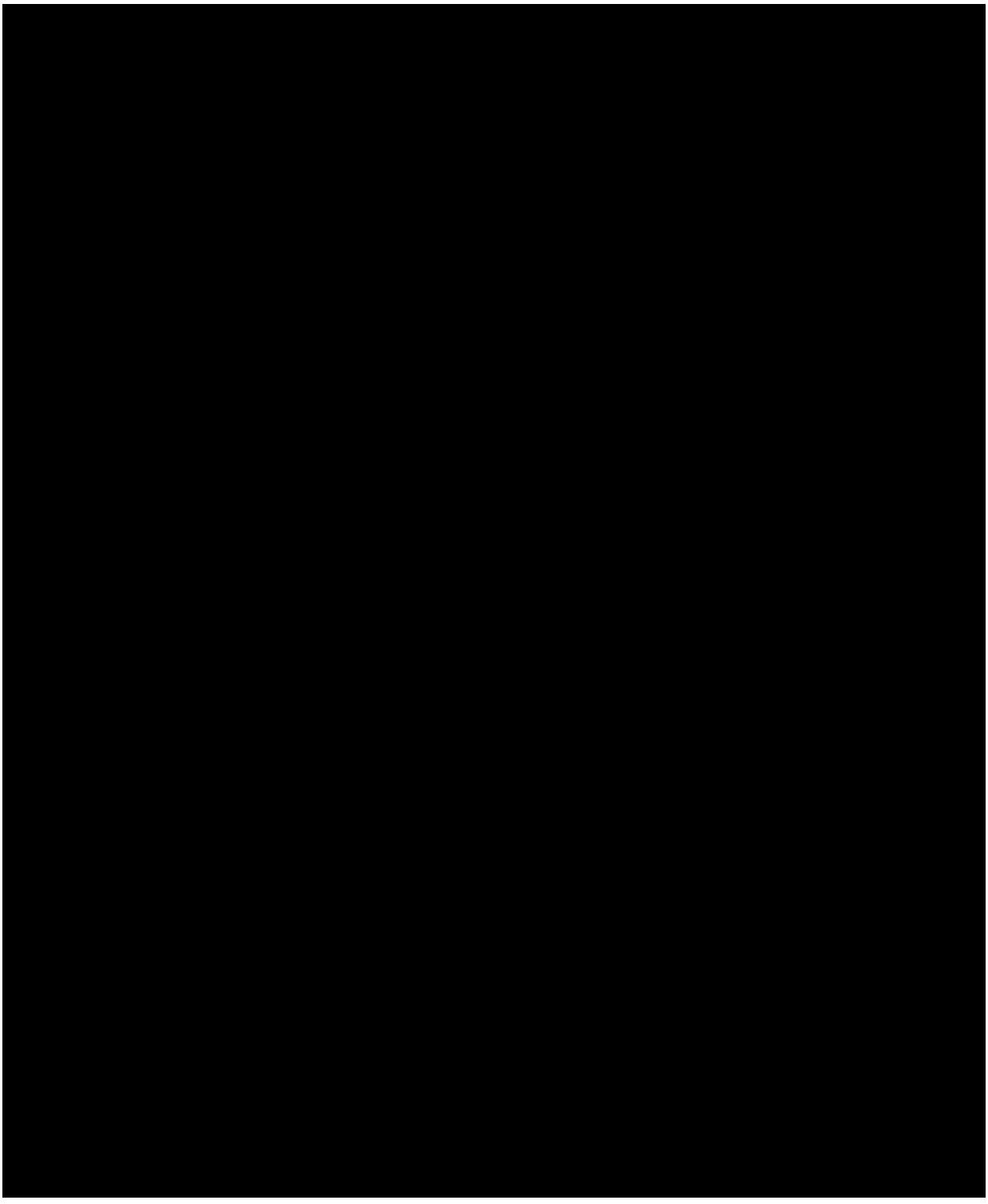
decline in performance status) symptomatic disease requiring rapid initiation of alternative systemic anti-cancer therapy.

Subjects who have received talimogene laherparepvec and completed the long term follow-up for any reason other than death or withdrawal of full consent and who provide consent and are eligible for a separate ongoing registry protocol may have the opportunity to follow-up for survival under this registry protocol which is in place for the long-term follow-up of subjects treated with talimogene laherparepvec in clinical trials. The registry protocol will also monitor for late and long-term adverse events thought to be potentially related to talimogene laherparepvec.

7.2.4 Reporting Exposure to Talimogene Laherparepvec

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 signs or symptoms suspected to be herpetic in origin or is 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.





7.4 Pharmacogenetic Studies

If the subject consents to the optional pharmacogenetic portion of this study, DNA analyses on blood samples 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. No additional samples are collected for this part of the study. DNA may be extracted from blood of subjects who consent to pharmacogenetic analyses.

7.5 Sample Storage and Destruction

Any blood or tumor samples collected according to the Schedule of Assessments (Table 8 through Table 13) 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, characterization of antibody response, and characterization of aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis 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 evaluations are not expected to be available in time to benefit the subject directly or to alter the treatment course, the results of qPCR testing from swabs of cold sores, vesicles, and other lesions suspected to be herpetic in origin will not be provided unless requested by the investigator or the subject. Results may not be available until the end of the study. [redacted]

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

[redacted] 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.

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 8 through Table 13) 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 8 through Table 13) 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 as described in Table 8 through Table 13.

Those subjects who discontinue investigational product should continue into long-term follow-up. Subjects in Part 1 will be followed for survival, talimogene laherparepvec related adverse events, and subsequent anticancer therapies every 12 weeks (± 28 days) for approximately 24 months after the last subject is enrolled in Part 1. Subjects in Part 2 will be followed for survival, talimogene laherparepvec related adverse events, pembrolizumab related adverse events (if applicable), and subsequent anticancer therapies every 12 weeks (± 28 days) for approximately 24 months after the last subject is enrolled per tumor type cohort.

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, publically 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(s) from investigational product 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(s) 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

Subjects can remain on either treatment if one is stopped prematurely assuming the subject meets criteria for continuing.

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

- subject request
- safety concern (eg, due to an adverse event)
- ineligibility determined
- protocol deviation
- non-compliance
- requirement for alternative therapy
- protocol-specified criteria (see Section 6.2.1.2)
- pregnancy
- death
- lost to follow-up
- decision by Sponsor (other than subject request, safety concern, lost to follow-up)
- disease progression

8.3.1.1 Discontinuation of Pembrolizumab treatment

- Subjects can receive up to 35 cycles (approximately 24 months) with pembrolizumab. During that time, subjects may continue until disease progression, or sponsor's decision to terminate the study.
- Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 weeks with systemic pembrolizumab and had at least 2 cycles of systemic pembrolizumab beyond the date when the initial CR was declared.

8.3.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- decision by sponsor
- 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 Definition of Disease Related Events

Disease related events are events (serious or non-serious) anticipated to occur in the study population due to the underlying disease. These could include events such as pain or discomfort caused by growing tumors due to overall worsening of disease. Such events do not meet the definition of an adverse event unless assessed to be more severe than expected for the subject's condition and/or if the investigator believes that the event is related to the investigational product(s)/study treatment/protocol required therapies.

All serious disease-related events will be recorded and reported to the sponsor or designee within 24 hours of the investigator's awareness of the event.

Disease-related events that would qualify as an adverse event or serious adverse event:

- An event based on the underlying disease that is worse than expected as assessed by the investigator for the subject's condition or if the investigator believes there is a causal relationship between the investigational product(s)/study treatment/protocol-required therapies and disease worsening, this must be reported as an adverse event or serious adverse event.

Disease-related events that do not qualify as adverse events or serious adverse events:

- An event which is part of the normal course of disease under study (eg, disease progression in oncology or hospitalization due to disease progression) is to be reported as a disease-related event.

Further, any disease related event which meets any of the seriousness criteria in Section 9.1.3 should be reported as a Serious Disease Related Event.

Note: For situations where disease related events are due to the subject's primary cancer, the primary tumor type (eg, metastatic hepatocellular carcinoma) should be used, rather than the term "disease progression".

9.1.2 Definition of 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 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.

Note: For situations where an adverse event due to the subject's primary cancer, the primary tumor type (eg, metastatic hepatocellular carcinoma) should be used, rather than the term "disease progression" .

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.

9.1.3 Definition of 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

A disease related event (eg, disease progression) is to be reported as a serious adverse event if:

- the subject's pre-existing condition becomes worse than what the investigator would consider typical for a subject with the same underlying condition, or
- if the investigator believes a causal relationship exists between talimogene laherparepvec and/or pembrolizumab and the event,
- and the event meets at least 1 of the serious criteria above.
- additionally, the investigator is required to report a fatal disease related event as serious adverse event

  *Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per the International Council for Harmonisation (ICH) definition, are reportable to Amgen in the same timeframe as serious adverse events to meet certain local requirements.

Therefore, these events are considered serious by Amgen for collection purposes.

- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose.

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, DILI, or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

9.2 Safety Event Reporting Procedures

9.2.1 Reporting Procedures for Disease Related Events

Disease-related events are defined in Section 9.1.1.

The investigator is responsible for ensuring that all disease related events (serious or non-serious) observed by the investigator or reported by the subject that occur after the first dose of talimogene laherparepvec or pembrolizumab through 30 (+7) days after the last dose of talimogene laherparepvec or pembrolizumab, whichever is later, are reported using the events CRF. Additionally, the investigator is required to report a fatal disease related event on the events CRF as a serious adverse event.

All serious disease-related events will be recorded and reported to the sponsor or designee within 24 hours. The investigator will submit any updated serious disease-related event data to the sponsor within 24 hours of it being available.

Disease-related events assessed by the investigator to be more severe than expected and/or related to the talimogene laherparepvec or pembrolizumab, and determined to be serious must be reported on the events CRF as serious adverse events and recorded and reported per Section 9.2.3. The investigator must assign the following attributes to each disease-related event:

- Disease-related event diagnosis or syndrome(s), if known (if not known, signs or symptoms),
- Dates of onset and resolution (if resolved),
- Did the event start prior to first dose of investigational product and other protocol-required therapies,
- Assessment of seriousness,
- Severity (and/or toxicity per protocol),
- Assessment of relatedness to talimogene laherparepvec/placebo and/or pembrolizumab, and/or study-mandated activity and/or procedures,
- Action taken, and
- Outcome of event

CTCAE version 4.03 will be used to grade a disease related event. The grading scale used in this study is described in Appendix A.

*Note: If the event is more severe than expected for the subject's condition or if the investigator believes there is a causal relationship between the investigational

product(s)/study treatment/protocol required therapies and disease worsening, the event should be reported as an adverse event, not a disease-related event.

The investigator is expected to follow reported disease-related events (serious or non-serious) until stabilization or reversibility.

9.2.2 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 the first dose of talimogene laherparepvec or pembrolizumab through 30 (+7) days after the last dose of talimogene laherparepvec or pembrolizumab, whichever is later, are reported using the applicable CRF (eg, events CRF).

All adverse events that occur after the consent form is signed but before enrollment must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure. Refer to Section 9.2.5.1 for management of hepatic events of clinical interest.

The investigator must assign the following attributes to each adverse event:

- adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms), dates of onset and resolution (if resolved),
- did the event start prior to first dose of investigational product and other protocol-required therapies,
- assessment of seriousness,
- severity (and/or toxicity per protocol),
- assessment of relatedness to talimogene laherparepvec and/or pembrolizumab,
- action taken, and
- outcome of event

The adverse event grading scale used will be the CTCAE version 4.03. The grading scale used in this protocol is described in Appendix A. The investigator must assess whether the adverse event is possibly related to the talimogene laherparepvec 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 talimogene laherparepvec and/or pembrolizumab”?

The investigator must assess whether the adverse event is possibly related to any study-mandated activity (eg, administration of talimogene laherparepvec and/or procedure [including any screening 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 (eg, administration of talimogene laherparepvec, 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 events CRF. The Investigator is expected to follow reported adverse events until stabilization or reversibility.

It is not acceptable for the investigator to send photocopies of the subject's medical records to (sponsor/responsible contact research organization [CRO]) in lieu of completion of the Events CRF page.

9.2.3 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events, follow up to a serious adverse event, including death due to any cause, observed by the investigator or reported by the subject that occur after signing of the informed consent through 90 (+7) days after the last dose of talimogene laherparepvec or pembrolizumab, 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 awareness of the event via the applicable CRF.

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 a paper Serious Adverse Event Contingency Report Form within 24 hours of the investigator's awareness

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 eSerious Adverse Event 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 talimogene laherparepvec or, if applicable, 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 talimogene laherparepvec"?

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"?

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, Events CRF).

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

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 (GCP).

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

9.2.3.1 Follow-up of Adverse Events and Serious Adverse Events

After the initial adverse event/serious adverse event report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All adverse events and serious adverse events will be followed until resolution, stabilization, until the event is otherwise explained, or the subject is lost to follow-up.

All new information for previously reported serious adverse events must be sent to Amgen within 24 hours following awareness of the new information. If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. Information provided about the serious adverse event must be consistent with that recorded on the Adverse Events CRF.

9.2.3.2 Reporting Serious Adverse Events After the Protocol-required Reporting Period

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period (as defined in Section 9.1.3) or after the end of study. However, these serious adverse events must be reported to Amgen (regardless of causality) if the investigator becomes aware of them. Per local requirements in some countries (eg, European Union [EU] member states), investigators are required to report serious adverse events that they become aware of after the end of study. If serious adverse events are reported, the investigator is to report them to Amgen within 24 hours following the investigator's awareness of the event.

Serious adverse events reported outside the protocol-required reporting period that occur during the long-term follow-up period until the end of study are to be captured in the Adverse Events CRF, although these events will not be considered treatment-emergent adverse events. Serious adverse events reported outside of the protocol-required reporting period that occur after the end of the study will be captured within the safety database as clinical trial cases for the purposes of expedited reporting.

9.2.3.3 Safety Monitoring Plan

Subject safety will be routinely monitored as defined in Amgen's safety surveillance and signal management processes.

9.2.4 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 enrollment, 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, or a procedure.

For the time period beginning at enrollment 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 ECI for this trial for Group A include:

- an overdose of pembrolizumab, as defined in Section 9.2.6.1
- an elevated AST or ALT lab value that is greater than or equal to 3x the ULN and an elevated TBL lab value that is greater than or equal to 2x the ULN and, at the same time, an ALP lab value that is less than 2x the ULN, 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. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

9.2.5 Information Related to Events of Clinical Interest Specifically for Group B HCC Subjects

9.2.5.1 Guidance for Management of Hepatic Events of Clinical Interest

Hepatic ECIs (HECIs) have been described in Section 9.2.6. All of these HECIs will require holding study intervention and notification of the Sponsor within 24 hours. All cases of retreatment after interruption of study intervention for HECI must be reported to the Sponsor and recorded in the database.

Immediate assessment in case of HECI:

<u>All Participants</u>

- All participants should be considered for evaluation according to the directions below within 72 hours of the alert for a non-overdose ECI. For lab assessments of HECIs, central laboratory is preferred; local laboratory is acceptable if central laboratory is not available.
- Procedures:
  - Consider obtaining a consultation with a hepatologist

- Obtain a work-up for hepatitis if there is no underlying hepatitis, including hepatitis A, B, C, D, E, Epstein-Barr virus, and cytomegalovirus
- Assess for ingestion of drugs/supplements with hepatotoxic potential
- Assess for alcohol ingestion
- Assess for potential bacterial infection, biliary obstruction, or occult gastrointestinal bleeding
- Repeat ALT, AST, total bilirubin, direct bilirubin, alkaline phosphatase, γ-glutamyl transpeptidase, INR, and complete blood count with differential
- Measure HCV RNA viral load (applies only for participants who have current active HCV infection or had infection in the past)
- HBV DNA, HBsAg, HBeAg, anti-HBc (total and IgM), anti-HBe, and anti-HBs regardless of prior HBV status (Note: participants should be questioned about compliance with the use of antiviral agents)
- Other laboratories or imaging studies as clinically indicated
- Consider liver biopsy if indicated

HCC patients are at risk for a range of complications that can cause hepatic laboratory abnormalities with or without clinical decompensation. Those with a history of chronic HCV or HBV infection also have the potential to experience virologic flares. Immune-related hepatitis has been observed in approximately 1-2% of participants who received pembrolizumab. The following section provides further guidance on the diagnosis and management of potential hepatic complications among HCC participants in this study. The recommendation is to hold pembrolizumab interventions and initiate per table.

Table 15. Management of Hepatic Events of Clinical Interest for Pembrolizumab:

	Diagnosis	Management
Hepatitis B consider flare or change in HBV immunologic status	Rapid elevation of ALT to > 5 x ULN and/or > 3x baseline	Interrupt pembrolizumab and talimogene laherparepvec intervention for up to 12 weeks. Start antiviral therapy or check for compliance if HBV is detectable. Measure safety labs for AST, ALT, ALP, T Bili, D Bili, and INR on weekly basis. Measure HBsAg and HBV DNA on weekly basis (if detected at the time of onset of ECI). Evaluate the following every 2-3 weeks: anti-HBe, HBe antigen, anti-HBs, and HBV DNA levels (if not detected at the onset of ECI) Restart pembrolizumab and talimogene laherparepvec intervention only if ALT returns to normal or Grade 1 (if normal at baseline), or to baseline grade (if Grade 2 at baseline) within 12 weeks, and the participant is clinically stable; otherwise, the participant should be permanently discontinued.
Hepatitis C exacerbation in participants with HCV RNA positive	Rapid elevation of ALT to > 5 x ULN and/or > 3x baseline	Interrupt pembrolizumab and talimogene laherparepvec intervention for up to 12 weeks. Assess use of injection or inhalation drugs. Recheck HCV genotype at the time of relapse of HCV RNA to rule out new infection. Measure safety labs for AST, ALT, ALP, T Bili, D Bili, and INR on weekly basis Measure HCV RNA levels every 2 weeks. Please discuss risk benefit with Sponsor prior to starting HCV antiviral therapy. Restart pembrolizumab and talimogene laherparepvec intervention only if ALT returns to normal or Grade 1 (if normal at baseline), or to baseline grade (if Grade 2 at baseline) within 12 weeks, and the participant is clinically stable; otherwise, the participant should be permanently discontinued.
Relapse of HCV infection for participants with successfully treated or new HCV infection	If HCV RNA was TND at baseline, and now has confirmed detectable HCV RNA (2 specimens, 1 week apart)	
Immune-related Hepatitis	If any of the HECI criteria is met as defined in the protocol Section Section 9.2.6	Interrupt pembrolizumab and talimogene laherparepvec study treatment for up to 12 weeks. Start IV corticosteroid 60 mg/day of prednisone or equivalent followed by oral corticosteroid. Monitor with biweekly laboratory tests, including AST, ALT, T Bili, D Bili, ALP, and INR.

Table 15. Management of Hepatic Events of Clinical Interest for Pembrolizumab:

	Diagnosis	Management
Immune-related Hepatitis (continue)	Note: Immune-related hepatitis is a diagnosis made after excluding other possible etiologies such as viral flare, biliary or vascular obstruction, infection, medications, and alcohol use usually immune-related hepatitis response to dechallenge and/or steroids and re-occurs with rechallenge	Restart pembrolizumab and talimogene laherparepvec intervention only if: a) Abnormal laboratory values resolve to Grade ≤ 1 or baseline (if abnormal at baseline) b) Taper steroid over 28 days c) Steroid treatment is tapered to prednisone < 10 mg/day or equivalent Permanently Discontinue pembrolizumab and talimogene laherparepvec intervention if: a) Laboratory abnormalities do not resolve within 3 weeks b) Steroids cannot be lowered to ≤ 10 mg/day (or prednisone equivalent) within 12 weeks c) Decompensation to CP-C status
Other Causes	Rule out infection with blood, urine, and ascites culture – antibiotics should be started if infection is found If total bilirubin is elevated, imaging should be obtained to rule out vascular compromise, biliary obstruction, and/or tumor progression by imaging Ruled out alcohol use and hepatotoxic drugs including herbal and alternative medications	Restart pembrolizumab and talimogene laherparepvec only if laboratory values have returned to Grade 1 or baseline (if normal or Grade 1 at start) or to baseline grade within 3 weeks. If biliary obstruction is present, consultation with a gastroenterologist and/or an interventional radiologist should be obtained to see if the obstruction may be relieved.

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9.2.6 Events of Clinical Interest for Group B HCC Subjects

Selected nonserious and serious adverse events are also known as ECIs and must be reported to the Sponsor.

Events of clinical interest for HCC subjects in this study include:

1. An overdose of Sponsor's product, as defined in Section 9.2.6.1, that is not associated with clinical symptoms or abnormal laboratory results.
2. Hepatic ECIs include any of the following events if the events are considered not due to disease progression as judged by the investigator. All of these events (if not associated with disease progression under study) will require holding study treatment, notification of the event(s) to the Sponsor within 24 hours after awareness via electronic media or paper.

For dose interval modification, refer to Section 6.2.2.2.1 and 6.2.2.2.2. For guidance related to the diagnosis and management of HECIs, refer to Section 9.2.5.1.

- ALT:
  a. Among subjects with Baseline ALT $<$ 2 x ULN: ALT $\geq$ 5 x ULN
  b. Among subjects with Baseline ALT $\geq$ 2 x ULN: ALT $>$ 3 x the Baseline level
  c. ALT $>$ 500 U/L regardless of baseline level
- Total Bilirubin:
  a. Total bilirubin $>$ 3.0 mg/dL
- Regardless of laboratory values, hepatic decompensation diagnosed clinically, including:
  - New onset clinically detectable ascites requiring intervention for $>$ 3 days
  - Hepatic Encephalopathy
  - Gastrointestinal bleeding suggestive of portal hypertension (e.g., esophageal or gastric varices

Progression of the cancer under study is not considered an ECI for pembrolizumab unless it is considered to be drug-related by the investigator.

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

For 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 9.2.2 and 9.2.3, 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 9.2.4.

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 4 months after the last dose of talimogene laherparepvec or pembrolizumab, whichever is later (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's Global Patient Safety within 24 hours of the investigator's awareness of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Forms (Appendix C). The Amgen's 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 Global Patient Safety 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 4 months after the last dose of talimogene laherparepvec or pembrolizumab, whichever is later (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's Global Patient Safety within 24 hours of the investigator's awareness 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.

Pregnancies and lactations that occur after the consent form is signed but before enrollment must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

9.4 Reporting Exposure to Talimogene Laherparepvec

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 signs or symptoms suspected to be herpetic in origin or is accidentally exposed to talimogene laherparepvec), while the subject is taking talimogene laherparepvec, 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 through 30 (+ 7) days after the last dose of talimogene laherparepvec.

Any potential or known unintended exposure should be reported to Amgen within 24 hours of the investigator's awareness 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 signs or symptoms suspected to be related to talimogene laherparepvec exposure, the exposed individual may be asked to have a swab taken from suspected lesions that are present to evaluate for the presence of talimogene laherparepvec DNA in the lesions by qPCR testing.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

Primary Endpoint:

Part 1:

Monotherapy cohorts 1-4: Subject incidence of DLTs with intrahepatic injection of talimogene laherparepvec into liver tumors in subjects with non-HCC with liver metastases and subjects with HCC without active viral hepatitis.

Combination cohorts 5 and 6: Subject incidence of DLTs with intrahepatic injection into liver tumors of talimogene laherparepvec in combination with systemic IV administration of pembrolizumab in subjects with non-HCC with liver metastases and subjects with HCC with and without viral hepatitis.

Part 2:

- ORR per modified irRC-RECIST with intralesional injection of talimogene laherparepvec into cutaneous, subcutaneous, lymph node, and liver tumors in combination with systemic IV administration of pembrolizumab separately by tumor type arm (hormone receptor positive BC, TNBC, CRC, CSCC, BCC, and HCC with and without viral hepatitis)
- Subject incidence, for each tumor type arm, of treatment-emergent and treatment-related adverse events, including DLTs

Secondary Endpoint(s):

Efficacy:

Part 1:

- ORR, BOR, DRR, DOR, response in injected and uninjected lesions, DCR, PFS, and OS separately for non-HCC and HCC tumors in monotherapy and combination cohorts

Part 2:

- BOR, DRR, DOR, response in injected and uninjected lesions, DCR, PFS, and OS by primary tumor type arm (hormone receptor positive BC, TNBC, CSCC, CRC, BCC, and HCC with and without viral hepatitis)

Safety:

Parts 1 and 2:

- Subject incidence of treatment-related and treatment-emergent adverse events in each monotherapy and combination cohorts in Part 1 and each tumor type separately in Part 2, and HCC with and without viral hepatitis in Part 2
- Subject incidence of detectable talimogene laherparepvec DNA in blood and urine

- Incidence of clearance of talimogene laherparepvec DNA from blood and urine
- Subject incidence (per subject) and rate of detection (per sample) of talimogene laherparepvec DNA and virus at the surface of injection site, the exterior of the occlusive dressing, and the oral mucosa
- Subject incidence of talimogene laherparepvec DNA detection in lesions suspected to be herpetic in origin

Exploratory Endpoint:

[redacted]

10.1.2 Analysis Sets

DLT Analysis Set: The DLT analysis set will include DLT-evaluable subjects enrolled in Part 1 defined as follows:

- Monotherapy Cohorts: Subjects who have had the opportunity to be on treatment for at least 6 weeks from the initial dosing of study treatment and have received at least 1 additional dose of talimogene laherparepvec
- Combination Cohorts: Subjects who have had the opportunity to be on treatment for at least 6 weeks from the initial dosing of study treatment, and have received at least 2 doses of talimogene laherparepvec and pembrolizumab in combination
- Subjects experiencing a DLT: Have a DLT during the DLT-evaluation period after at least 1 dose of talimogene laherparepvec (for monotherapy cohorts) and talimogene laherparepvec and pembrolizumab (for combination cohorts)

Full Analysis Set: For efficacy analyses of talimogene laherparepvec monotherapy, the full analysis set will be defined as all subjects who received at least 1 dose of talimogene laherparepvec and no treatment with systemic pembrolizumab, and for efficacy analyses of talimogene laherparepvec in combination with systemic pembrolizumab, it will be defined as all subjects who received at least 1 dose of talimogene laherparepvec and at least 1 dose of pembrolizumab in combination.

Safety Analysis Set: The safety analysis set will be defined as all subjects who received study therapy. For monotherapy cohort, subjects will be included for analysis of safety if they received at least 1 dose of talimogene laherparepvec. For the combination therapy cohorts or part 2, subjects will be included for analysis of safety if they received at least 1 dose of talimogene laherparepvec or at least 1 dose of pembrolizumab.

[redacted]

Covariates and Subgroups

The following covariates may be used whenever applicable to examine efficacy and safety in subgroups or in multivariate analyses:

- Region, if applicable (USA vs non-USA)
- Age at baseline (< 50, ≥ 50; < 65, ≥ 65; < 75, ≥ 75 years)
- Baseline LDH ($\leq$ ULN vs $>$ ULN)
- Gender (Female vs Male)
- Baseline ECOG (0 vs 1)
- Baseline sum of lengths of measurable lesions
- Baseline sums of lengths of measurable liver lesions
- Prior exposure to chemo therapy (Yes vs No)
- HSV-1 serostatus (Yes vs No)
- Maximum talimogene laherparepvec volume at highest concentration per visit (≤ 4 mL vs > 4 mL)
- Baseline HBV or HCV status
- Baseline Microsatellite Instability status for CRC subjects

10.2 Sample Size Considerations

Sample Size Considerations for Part 1

The sample size of approximately 3 to 6 subjects per monotherapy cohort is determined empirically and is consistent with those used in traditional "3+3" phase 1 designs to evaluate safety assuming a true DLT rate of less than 1/3. There are up to 4 monotherapy cohorts in Groups A / B in Part 1. Subjects enrolled in a monotherapy cohort may be replaced if they are not evaluable for DLT (eg, did not receive talimogene laherparepvec or ended the study treatment before completion of the DLT evaluation period for a reason other than experiencing a DLT). Table 16 summarizes the probability of declaring a monotherapy cohort safe or unsafe for a range of true cohort DLT probabilities.

Table 16. Probability of Declaring a Monotherapy Cohort Safe or Unsafe

True Cohort DLT Probability	Probability Declare Cohort Safe	Probability Declare Cohort Unsafe
0.1	0.91	0.09
0.2	0.71	0.29
0.3	0.49	0.51
0.4	0.31	0.69
0.5	0.17	0.83

DLT = dose-limiting toxicity

Safety of the combination will be evaluated with the mTPI up-and-down design in Part 1 to determine the talimogene laherparepvec MTC with a target DLT rate of 40%. The maximum sample size in the combination cohorts 5 and 6 or 6a will be 28 (maximum of 12 DLT evaluable subjects, evaluated at 6b). Unless the cohort 5 is deemed too toxic, patients may be enrolled and assigned to appropriate doses until the maximum sample size is reached or minimum of 12 subjects are enrolled in Cohort 6 provided the mTPI outcome is not at a D or DU in cohort 6. If in HCC group, cohort 6b completes prior to cohorts 5 and 6a enrollment, and 6b is deemed safe, then cohorts 5 and 6a will close to enrollment. Full details of the mTPI will be specified in the DLRT Charter.

Table 17. mTPI Dose Decision Outcomes With a 40% Target DLT Rate[a,b,c]

Number of toxicities	Number of patients treated at current dose																				
	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
0	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
1	S	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
2	S	S	S	S	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
3	D	S	S	S	S	S	S	S	E	E	E	E	E	E	E	E	E	E	E	E	E
4	DU	DU	D	S	S	S	S	S	S	S	S	S	E	E	E	E	E	E	E	E	E
5		DU	DU	DU	D	S	S	S	S	S	S	S	S	S	S	E	E	E	E	E	E
6			DU	DU	DU	D	D	S	S	S	S	S	S	S	S	S	S	S	E	E	E
7				DU	DU	DU	DU	D	D	S	S	S	S	S	S	S	S	S	S	S	S
8					DU	DU	DU	DU	DU	D	D	S	S	S	S	S	S	S	S	S	S
9						DU	DU	DU	DU	DU	DU	D	D	S	S	S	S	S	S	S	S
10							DU	DU	DU	DU	DU	DU	DU	D	S	S	S	S	S	S	S
11								DU	DU	DU	DU	DU	DU	DU	DU	D	S	S	S	S	S
12									DU	DU	DU	DU	DU	DU	DU	DU	DU	D	S	S	S
13										DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	D	S
14											DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
15												DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
16													DU	DU	DU	DU	DU	DU	DU	DU	DU
17														DU	DU	DU	DU	DU	DU	DU	DU
18															DU	DU	DU	DU	DU	DU	DU
19																DU	DU	DU	DU	DU	DU
20																	DU	DU	DU	DU	DU
21																		DU	DU	DU	DU
22																			DU	DU	DU
23																				DU	DU
24																					DU

E = Escalate to the next higher dose
S = Stay at the current dose
D = De-escalate to the next lower dose
U = The current dose is unacceptably toxic
MTD = 40%

DLRT = Dose Level Review Team; DLT = dose limiting toxicity; MTD = Maximum tolerated dose; modified toxicity probability interval

[a] Vertical axis is the maximum allowed subject incidence of DLT among the number of DLT-evaluable subjects on the horizontal axis

[b] First DLRT evaluation is planned after the first 4-6 subjects have been enrolled with a minimum of 4 DLT evaluable subjects. DLRT evaluation may occur earlier at the DLRT's discretion. Please see details in the DLRT charter.

[c] Sample Size = 28 across cohorts 5 and 6

Part 2 for non-HCC tumor types (Group A) or HCC (Group B) will open if the corresponding group MTC is selected at the end of Part 1.

The probability of selecting 10^8 PFU/mL as the MTC in Part 2 for Group A/B is 97% (3% for selection of 10^7 PFU/mL) if the true DLT rate is 10% for 10^7 PFU/mL and 30% for 10^8 PFU/mL, respectively (Table 17).

Table 18. MTC Selection Probabilities For True DLT Rate Scenarios

True Cohort DLT Probability		Probability of Selection		
10^7	10^8	10^7	10^8	No RP2D
0.01	0.05	0.00	1.00	0.00
0.05	0.25	0.01	0.99	0.00
0.15	0.25	0.04	0.96	0.00
0.1	0.3	0.03	0.97	0.00
0.3	0.4	0.40	0.58	0.02
0.3	0.6	0.73	0.25	0.02
0.4	0.5	0.66	0.21	0.13
0.6	0.6	0.23	0.02	0.76

DLT = dose-limiting toxicity; HCC = hepatocellular carcinoma; MTC = maximum tolerated concentration; mTPI = modified toxicity probability interval; RP2D = recommended phase 2 dose

[a] Assumptions: Maximum 28 DLT-evaluable subjects in each group (non-HCC vs HCC); 40% target DLT rate; 4 additional subjects prior to each analysis.

Sample Size Considerations for Part 2

The recommended phase 2 dose from Part 1 (RP2D) for non-HCC (Group A) and HCC (Group B) will be evaluated in Part 2 independently for each tumor type arm for the combination of talimogene laherparepvec with systemic pembrolizumab. Subjects that initiate treatment at the corresponding RP2D in Part 1 will not be included in the Part 2 efficacy analysis according to their respective tumor type arm.

The primary objective in Part 2 for each tumor type arm will be to evaluate the ORR per modified irRC-RECIST with a minimum potential follow-up of at least 29 weeks. The null hypothesis (H0) for each tumor type is an ORR $\leq$ 10% which, if true, would not warrant further evaluation in contrast to the alternative hypothesis (H1) of an ORR $\geq$ 40%.

The following 2-stage design will be used to reject H0 at a $\leq$ 2.5% 1-sided significance level. The efficacy analysis will be based on the Full Analysis Set in Part 2 only.A cumulative total of 10 subjects will be treated in Stage 1 and enrollment is planned to stop. If there are 2 or more responders (PR or CR no confirmation is needed), then a total of 11 additional subjects will be treated in Stage 2; otherwise, H0 will be accepted and enrollment will be permanently discontinued. If the required number of responders to continue to Stage 2 is observed before the end of Stage 1 enrollment, then enrollment will not be suspended.

H0 will be rejected after Stage 2 if there are $\geq$ 6 responders (with confirmation) in 21 treated subjects, ie, the observed ORR is $\geq$ 28.6%. In the event precisely 21 subjects are not included in the analysis in total, H0 will be rejected if the lower limit of the

95% exact binomial CI is > 10% (Atkinson and Brown, 1985). If exactly 10 and 11 subjects are included at Stage 1 and 2, respectively, the design achieves a 1-sided 1.3% significance level, 88.4% power, and the probability of stopping at Stage 1 if H0 (H1) is true is 73.6% (4.6%).

For each tumor type that advances to Stage 2, a Bayesian framework will be utilized to assess evidence that the combination ORR exceeds that expected for pembrolizumab alone to aid in decision-making as to whether further evaluation is warranted. Further detail will be described in the Statistical Analysis Plan.

From 10 to 21 subjects per tumor type are expected to be treated at the RP2D for a total of 60 to 126 subjects.

For Part 2, the DLRT will consider prospective guidelines in the DLRT Charter to monitor safety separately by tumor type arm and, if introduced, talimogene laherparepvec total volumes > 4 mL within Group A and Group B.

The subject incidence of DLT in Part 2 will be based on the DLT Analysis Set with at least 6 weeks minimum potential follow-up.

The maximum total sample size for Parts 1 and 2 **is 127** subjects (**74** subjects in Part 1; **53** subjects in Part 2). Dose-limiting toxicity non-evaluable subjects will not be replaced in Part 2.

10.3 Planned Analyses

10.3.1 Interim Analyses

Dose-limiting toxicities interim safety analyses will be performed to support the evaluation of safety and determination of the MTC and MTV of talimogene laherparepvec administered as monotherapy and in combination with systemic pembrolizumab. Interim efficacy analysis for part 1 will be performed as needed Interim safety and efficacy futility analyses are planned for this study in Part 2 separately for each tumor type arm.

10.3.1.1 DLT Safety Analysis (Part 1)

The planned interim safety data reviews for monotherapy cohorts in Part 1 to evaluate the subject incidence of DLTs will be conducted according to timing/rules described in Table 1 (Section 3.1.1). Data will be reviewed by a DLRT. The DLRT will recommend either to declare the cohort dose intolerable, to reassess safety after 3 additional

DLT-evaluable subjects, or to declare the cohort dose tolerable and to apply the same evaluation rules to subsequent cohorts.

For combination cohorts in Part 1, the DLRT will recommend according to the DLRT Charter whether it is safe to continue enrollment based on the mTPI up-and-down design.

10.3.1.2 Interim Safety Analysis (Part 2)

An interim safety data review will occur for each tumor type separately after approximately 10 subjects have been treated in Part 2 with the specific tumor type with at least 6 weeks of follow-up.

Additional safety analyses may be conducted as warranted during Part 2 if a DLT event occurs in the first 4 DLT-evaluable subjects or after a target of approximately 6 and 16 DLT-evaluable subjects. As appropriate the DLRT will be convened to monitor safety.

A total volume $>$ 4 mL of talimogene laherparepvec may be allowed in Part 2 with systemic pembrolizumab if it is declared safe without pembrolizumab in Part 1. In this event, the DLRT will also monitor safety in Part 2 separately among subjects in non-HCC (Group A) and HCC (Group B) arms that receive at least 1 dose of talimogene laherparepvec with a total volume $>$ 4 mL at the combination MTC with systemic pembrolizumab. Subjects will be included in the safety assessment of $>$ 4 mL with at least 3 weeks follow-up from an initial total volume $>$ 4 mL at the combination MTC.

Safety analyses, including analyses of the subjects receiving a total volume $>$ 4 mL talimogene laherparepvec, will be performed at the time of the planned analyses for each tumor type arm or more frequently at the DLRTs discretion.

10.3.1.3 Interim Futility Analysis (Part 2)

One interim efficacy futility analysis will occur after 10 subjects have been treated with the combination in Part 2 by tumor type and have had an opportunity to be followed up for at least 20 weeks. Enrollment will be suspended for the specific tumor type pending the outcome of the interim analysis. If there are 2 or more responders (CR or PR confirmation not required), then a total of 11 additional subjects will be treated; otherwise, further enrollment of the tumor type arm will be permanently discontinued. If at least 2 responders are observed by the enrollment of the 10th treated subject, then enrollment will not be suspended.

10.3.2 Dose Level Review Team (DLRT)

A DLRT consisting of the Amgen study team, including at least one medical clinician, safety representative and biostatistician, at least one representative of the Merck study team, and at least one participating investigator who has recruited subjects into Part 1, will review the safety data to evaluate possible DLTs. Representative(s) from Merck will participate in DLRT meetings for all cohorts (voting member only for Cohorts 5 and 6 of Part 1 and all cohorts of Part 2). The DLRT will make recommendations in Part 1 and 2 according to a DLRT Charter. The DLRT Charter will include guidelines to monitor safety in Part 2 separately by tumor type arm and, if introduced, talimogene laherparepvec total volumes $>$ 4 mL within Group A and Group B. In Part 2, the DLRT may consider reducing the RP2D talimogene laherparepvec concentration and/or discontinuation of total volumes $>$ 4 mL, if introduced.

10.3.3 Primary Analysis

One clinical study report (CSR) will be written based on the results of the primary analyses across Part 1 and Part 2.

Primary Analysis: The primary analysis for each combination cohort from Part 2 will occur independently when all subjects in each tumor type arm have a minimum potential follow-up of $\geq$ 29 weeks. The primary analysis for part 1 will occur after all subjects have a minimum potential follow-up of $\geq$ 29 weeks.

10.3.4 Final Analysis

Final Analysis: The final analysis will occur when all subjects have discontinued the study treatment and have had the opportunity to complete the long-term survival follow-up. One CSR will be written with the updated results from the final analyses at the completion of the study.

10.4 Planned Methods of Analysis

The data will be analyzed by cohort/group (non-HCC and HCC), in the overall population and by tumor type, if applicable.

Descriptive statistics will be provided for demographic, safety, efficacy and [redacted] endpoints. Formal analysis will be performed on the primary endpoints in Part 2.

A separate comprehensive Statistical Analysis Plan will be developed.

10.4.1 Primary Endpoint

Part 1:

The DLT analysis set will be used to summarize the subject incidence of DLT for the study and the safety analysis set will be used for all other analyses of safety endpoints (including but not limited to all adverse events, grade ≥ 3 adverse events, serious adverse events, fatal adverse events, adverse events requiring discontinuation of study drug, and adverse events defined as events of interest). For talimogene laherparepvec monotherapy, safety will be assessed for non-HCC (Group A) and HCC (Group B) groups based on the "3 + 3" design. For the combination of talimogene laherparepvec with pembrolizumab, safety will be assessed for non-HCC (Group A) and HCC (Group B) groups based on the mTPI up-and-down design.

Part 2

The 2 stage efficacy analysis will be conducted using the full analysis set from Part 2, unless otherwise specified. The 2-stage design will be used to evaluate the ORR per the modified irRC-RECIST. The null hypothesis of a 10% ORR for a given tumor type that continued to Stage 2 will be rejected if an exact binomial 95% CI for the ORR is above 10% (Atkinson and Brown, 1985). The primary analysis of efficacy will include subjects that receive at least 1 dose of talimogene laherparepvec and at least 1 dose of pembrolizumab in combination from Part 2.

For each tumor type that advances to Stage 2, a Bayesian framework will be utilized to assess evidence that the combination ORR exceeds that expected for pembrolizumab alone to aid in decision-making as to whether further evaluation is warranted. Further detail will be described in the Statistical Analysis Plan.

10.4.2 Secondary Endpoints

Efficacy Endpoints:

Part 1:

Objective response rate, BOR, DRR, DOR, response in injected and uninjected lesions, DCR, PFS, and OS will be summarized separately for non-HCC and HCC tumors in monotherapy cohorts and combination cohorts. Objective response rate, DRR, and DCR will be summarized with an associated 95% CI. Duration of response among responders, PFS and OS will be estimated using the Kaplan-Meier method. A listing of efficacy endpoints will be provided for whichever combination cohort is not the RP2D, if applicable.

Part 2:

BOR, DRR, DOR, response in injected and uninjected lesions, DCR, PFS, and OS will be summarized by primary tumor type arm (hormone receptor positive BC, TNBC, CRC, CSCC, BCC, and HCC with and without viral hepatitis). Objective response rate, DRR, and DCR will be summarized with an associated 95% CI. Duration of response among responders, PFS and OS will be estimated using the Kaplan-Meier method. Tumor response endpoints may also be evaluated based on modified RECIST v 1.1 for historical comparison for each tumor type that continues to Stage 2 of Part 2.

Safety Endpoints (Parts 1 and 2):

Subject incidence of treatment-emergent and treatment-related adverse events (monotherapy and combination cohorts in Part 1 and each tumor type arm separately in Part 2; including all treatment-emergent adverse events, grade ≥ 3 adverse events, serious adverse events, adverse events of interest and events requiring the discontinuation of study drug, and 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 4.03 will be used to grade severity of adverse events.

Subject incidence of all disease related events, fatal disease related events, serious disease related events, disease related events leading to withdrawal from study drug, and significant disease related events will also be provided.

A summary of deaths after initiation of the study through 90 days since the last dose of talimogene laherparepvec or pembrolizumab, whichever is discontinued last will be provided.

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.

Summary statistics will be provided for vital signs, physical measurements and laboratory data, details of the analysis will be provided in statistical analysis plan.

10.4.3 Exploratory Endpoints

[redacted]

[redacted]

10.5 Handling of Missing and Incomplete Data

Partial or missing dates of adverse events and concomitant medications will be imputed. Adverse events with missing severity and/or possible relationship to talimogene laherparepvec will be included in the all adverse events analyses, except by severity grade and treatment-related. Every effort will be made to obtain complete dates for deaths. Details of the imputation algorithms will be specified in the study-specific statistical analysis plan.

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

An initial sample ICF 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 subject 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 product is 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 is to be documented in the subject's medical records, and the ICF is to be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The original signed ICF 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 and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the ICF to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the ICF to attest that informed consent was freely given and understood.

11.2 Institutional Review Board/Independent Ethics Committee

A copy of the protocol, proposed ICF, 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 ICF 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 adverse event 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 ICFs) are to be kept in confidence by the investigator, except as described below.

In compliance with Federal regulations/International Council for Harmonization (ICH)/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, a treatment group, cohort or arm 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(s) 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(s) and by what mechanism, after termination of the study and before the product(s) is/are 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 IVR system captures the following data points and these are considered source data: subject identification.

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 the following:

- subject files containing completed CRFs, ICFs, and subject identification list
- study files containing the protocol with all amendments, **IB**, 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 Research & Development Compliance and Audit 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:

- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- 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, data queries and/or site notifications are created in the EDC system database for site resolution and subsequently closed by the EDC system or by an Amgen reviewer.
- All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data, centrally or adjudicated data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

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 8 through Table 13), the investigator can search publically 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

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 encourages 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.

13. REFERENCES

Abou-Alfa GK, Meyer T, Cheng AL, et al. Cabozantinib in Patients with Advanced and Progressing Hepatocellular Carcinoma. *N Engl J Med.* 2018;379(1):54-63.

Abrams HL, Spiro R, Goldstein N. Metastases in carcinoma. Analysis of 1000 autopsied cases. *Cancer.* 1950; 3(1):74-85.

Andtbacka RHI, Collichio FA, Amatruda T, et al. OPTiM: a randomized phase III trial of talimogene laherparepvec (T-VEC) versus subcutaneous (SC) granulocyte-macrophage colony-stimulating factor (GM-CSF) for the treatment (tx) of unresected stage IIIB/C and IV melanoma. *J Clin Oncol*. 2013;31(suppl). Abstract LBA9008.

Andtbacka RHI, Ross MI, Delman K, et al. Responses of injected and uninjected lesions to intralesional talimogene laherparepvec (T-VEC) in the OPTiM study and the contribution of surgery to response. Society of Surgical Oncology Cancer Symposium in Phoenix, Arizona March 12-15, 2014. Abstract 52.

Atkinson AN and Brown BW. Confidence Limits for Probability of Response in Multistage Phase II Clinical Trials. *Biometrics*. 1985;41 : 741-744.

Bellati F, Visconti V, Napoletano C, Antonilli M, Frati L, Panici PB, et al. Immunology of gynecologic neoplasms: analysis of the prognostic significance of the immune status. *Curr Cancer Drug Targets*. 2009; 9(4): 541-565.

Blank C, Brown I, Peterson AC, Spiotto M, Iwai Y, Honjo T, et al. PD-L1/B7H-1 inhibits the effector phase of tumor rejection by T cell receptor (TCR) transgenic CD8+ T cells. *Cancer Res.* 2004;64(3):1140-1145.

Bremnes RM, Al-Shibli K, Donnem T, Sirera R, Al-Saad S, Andersen S, et al. The role of tumor-infiltrating immune cells and chronic inflammation at the tumor site on cancer development, progression, and prognosis: emphasis on non-small cell lung cancer. *J Thorac Oncol*. 2011;6(4):824-833.

Bruix J, Qin, S, Merle, P, Granito, A, Huang, Y-H, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE) : a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet*. 2017;389(10064):56-66.

Chang KJ, Senzer NN, Binmoeller K, et al. Phase I dose-escalation study of talimogene laherparepvec (T-VEC) for advanced pancreatic cancer (ca). *J Clin Oncol*. 2012; 30(suppl; abstract e14546).

Chang WJ, Du Y, Zhao X, Ma LY, Cao GW. Inflammation-related factors predicting prognosis of gastric cancer. *World J Gastroenterol*. 2014;20(16):4586-4596.

Cheng X, Veverka V, Radhakrishnan A, Waters LC, Muskett FW, Morgan SH, et al. Structure and interactions of the human programmed cell death 1 receptor. *J Biol Chem*. 2013;288(17):11771-11785.

Chesney J, Collichio F, Andtbacka RHI, et al. 1108PD - Interim safety and efficacy of a randomized (1:1), open-label phase 2 study of talimogene laherparepvec (T) and ipilimumab (I) vs I alone in unresected stage IIIB-IV melanoma. *Annals of Oncology*. 2016;27(6):379-400.

Conti L, Gessani S. GM-CSF in the generation of dendritic cells from human blood monocyte precursors: recent advances. *Immunobiology*. 2008;213(9-10):859-870.

Curran MA, Montalvo W, Yagita H, Allison JP. PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors. *Proc Natl Acad Sci U S A*. 2010;107(9):4275-4280.

Demir G, Klein HO, Tuzuner N. Low dose daily rhGM-CSF application activates monocytes and dendritic cells in vivo. *Leuk Res*. 2003;27(12):1105-1108.

Disis ML. Immune regulation of cancer. *J Clin Oncol*. 2010;28(29):4531-4538.

Dunn GP, Dunn IF, Curry WT. Focus on TILs: Prognostic significance of tumor infiltrating lymphocytes in human glioma. *Cancer Immun*. 2007;7:12.

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours : Revised RECIST guideline (version 1.1). Eur J Cancer. 2009; 45:228-247.

El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet*. 2017. http://dx.doi.org/10.1016/S0140-6736, (17)31046-31052.

Finn RS, Ryoo B-Y, Merle P, et al. Results of KEYNOTE-240: phase 3 study of pembrolizumab (Pembro) vs best supportive care (BSC) for second line therapy in advanced hepatocellular carcinoma (HCC). *J Clin Oncol*. 2019;37(15_suppl):4004-4004.

Geevarghese SK, Geller DA, de Haan HA, et al. Phase I/II study of oncolytic herpes simplex virus NV1020 in patients with extensively pretreated refractory colorectal cancer metastatic to the liver. *Hum Gene Ther*. 2010;21:1119-1128.

Gogas HJ, Ribas A, Chesney J, et al. MASTERKEY-265: A phase III, randomized, placebo (Pbo)-controlled study of talimogene laherparepvec (T) plus pembrolizumab (P) for unresectable stage IIIB–IVM1c melanoma (MEL). *Annals of Oncology*. 2021;32 (suppl_5):S867-S905. 10.1016/annonc/annonc706.

Gooden MJ, de Bock GH, Leffers N, Daemen T, Nijman HW. The prognostic influence of tumour-infiltrating lymphocytes in cancer: a systematic review with meta-analysis. *Br J Cancer*. 2011;105(1):93-103.

Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation. US Department of Health and Human Services, Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CEBR), July 2009.

Hammond ME, Hayes DF, Dowsett M, et al. American society of clinical oncology/college of American pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. *J Clin Oncol*. 2010;28(16):2784-2795.

Hart DN. Dendritic cells: unique leukocyte populations which control the primary immune response. *Blood*. 1997;90(9):3245-3287.

Heo H, Reid T, Ruo L, et al. Randomized dose-finding clinical trial of oncolytic immunotherapeutic vaccinia JX-594 in liver cancer. *Nat Med*. 2013;19(3):329-336.

Hirano F, Kaneko K, Tamura H, Dong H, Wang S, Ichikawa M, et al. Blockade of B7-H1 and PD-1 by monoclonal antibodies potentiates cancer therapeutic immunity. *Cancer Res*. 2005;65(3):1089-1096.

Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med*. 2010;363(8):711-723.

Huang X, Venet F, Wang YL, Lepape A, Yuan Z, Chen Y, et al. PD-1 expression by macrophages plays a pathologic role in altering microbial clearance and the innate inflammatory response to sepsis. *Proc Natl Acad Sci U S A*. 2009;106(15):6303-6308.

Ikeda H, Chamoto K, Tsuji T, et al. The critical role of type-1 innate and acquired immunity in tumor immunotherapy. *Cancer Sci*. 2004;95(9):697-703.

Karim R, Jordanova ES, Piersma SJ, Kenter GG, Chen L, Boer JM, et al. Tumor-expressed B7-H1 and B7-DC in relation to PD-1+ T-cell infiltration and survival of patients with cervical carcinoma. *Clin Cancer Res*. 2009;15(20):6341-6347.

Kaufman HI, Andtbacka HI, Collichio FA, et al. Primary OS from OPTiM, a randomized phase 3 trial of talimogene laherparepvec vs. subcutaneous granulocyte-macrophage colony-stimulating factor for the treatment of unresected stage IIIB/C and IV melanoma. ASCO Annual Meeting, 2014, Abstract 9008a.

Kaufman HL, Kim DW, DeRaffele, G, Mitcham J, Coffin RS, Kim-Schulze S. Local and distant immunity induced by intralesional vaccination with an oncolytic herpes virus encoding GM-CSF in patients with stage IIIc and IV melanoma. *Ann Surg Oncol*. 2010;17(3):718-730.

Keir ME, Butte MJ, Freeman GJ, Sharpe AH. PD-1 and its ligands in tolerance and immunity. *Annu Rev Immunol*. 2008;26:677-704.

Kim ST, Jeong H, Woo OH, Seo JH, Kim A, Lee ES, et al. Tumor-infiltrating lymphocytes, tumor characteristics, and recurrence in patients with early breast cancer. *Am J Clin Oncol*. 2013;36(3):224-231.

Kirk R. Risk factors. CD8+:FOXP3+ cell ratio is a novel survival marker for colorectal cancer. *Nat Rev Clin Oncol*. 2010;7(6):299.

Knutson KL, Disis ML. Tumor antigen-specific T helper cells in cancer immunity and immunotherapy. *Cancer Immunol Immunother*. 2005;54(8):721-728.

Kudo, M, Finn RS, Qin S, et al. Lenvatinib Versus Sorafenib in First-Line Treatment of Patients with Unresectable Hepatocellular Carcinoma: A Randomised Phase 3 Non-Inferiority Trial. *Lancet* 391, no. 10126 (Mar 24 2018): 1163-73

Lázár-Molnár E, Yan Q, Cao E, Ramagopal U, Nathenson SG, Almo SC. Crystal structure of the complex between programmed death-1 (PD-1) and its ligand PD-L2. *Proc Natl Acad Sci U S A*. 2008;105(30):10483-10488.

Lin DY, Tanaka Y, Iwasaki M, Gittis AG, Su HP, Mikami B, et al. The PD-1/PD-L1 complex resembles the antigen-binding Fv domains of antibodies and T cell receptors. *Proc Natl Acad Sci U S A*. 2008;105(8):3011-3016.

Liu BL, Robinson M, Han Z-Q, et al. ICP34.5 deleted herpes simplex virus with enhanced oncolytic, immune stimulating, and anti-tumour properties. *Gene Therapy*. 2003; 10:292-303.

Liu F, Lang R, Zhao J, Zhang X, Pringle GA, Fan Y, et al. CD8(+) cytotoxic T cell and FOXP3(+) regulatory T cell infiltration in relation to breast cancer survival and molecular subtypes. *Breast Cancer Res Treat*. 2011;130(2):645-655.

Llovet JM, Rici S, Mazzaferro V, et al. Sorafenib in Advanced Hepatocellular Carcinoma. *N Engl J Med*. 2008; 359:378-390.

Long GV et al. A phase 1/3 multicenter trial of talimogene laherparepvec in combination with pembrolizumab for unresected, stage IIIB-IV melanoma (MASTERKEY-265). *J Clin Oncol.*2016;34 (suppl; abstr TPS9598).

Lonial S. Immunomodulation: the role of hematopoietic cytokines. *Support Cancer Ther*. 2004;1(2):80-88.

Mathai AM, Kapadia MJ, Alexander J, Kernochan LE, Swanson PE, Yeh MM. Role of Foxp3-positive tumor-infiltrating lymphocytes in the histologic features and clinical outcomes of hepatocellular carcinoma. *Am J Surg Pathol*. 2012;36(7):980-986.

Mei Z, Liu Y, Liu C, et al. Tumour-infiltrating inflammation and prognosis in colorectal cancer: systematic review and meta-analysis. *Br J Cancer*. 2014;110(6):1595-1605.

Nguyen LT, Ohashi PS. Clinical blockade of PD1 and LAG3 – potential mechanisms of action. *Nat Rev Immunol*. 2014; 15:45-56.

Nishimura H, Agata Y, Kawasaki A, Sato M, Imamura S, Minato N, et al., Developmentally regulated expression of the PD-1 protein on the surface of double-negative (CD4-CD8-) thymocytes. *Int Immunol*. 1996;8(5):773-780.

Nishimura T, Nakui M, Sato M, et al. The critical role of Th1-dominant immunity in tumor immunology. *Cancer Chemother Pharmacol*. 2000;46(suppl):S52-S61.

Nishino M, Gargano, M, Suda M, Ramaiya NH, Hodi FS. Optimizing immune-related tumor response assessment: does reducing the number of lesions impact response assessment in melanoma patients treated with ipilimumab. *J Immunother Cancer*. 2014;2(17);1-12.

Nomi T, Sho M, Akahori T, Hamada K, Kubo A, Kanehiro H, et al. Clinical significance and therapeutic potential of the programmed death-1 ligand/programmed death-1 pathway in human pancreatic cancer. *Clin Cancer Res*. 2007;13(7):2151-2157.

Nosho K, Baba Y, Tanaka N, Shima K, Hayashi M, Meyerhardt JA, et al. Tumour-infiltrating T-cell subsets, molecular changes in colorectal cancer, and prognosis: cohort study and literature review. *J Pathol*. 2010;222(4):350-366.

Oble DA, Loewe R, Yu P, Mihm MC Jr. Focus on TILs: prognostic significance of tumor infiltrating lymphocytes in human melanoma. *Cancer Immun*. 2009;9:3.

Ott PA, Hodi FS, Robert C. CTLA-4 and PD-1/PD-L1 blockade: new immunotherapeutic modalities with durable clinical benefit in melanoma patients. *Clin Cancer Res*. 2013;19(19):5300-5309.

Park BH, Hwang T, Liu TC, et al. Use of a targeted oncoytic poxvirus, JX-594, in patients with refractory primary or metastatic liver cancer: a phase I trial. *Lancet Oncol*. 2008; 9:533-42.

Patel JK, Didolkar MS, Pickren JW, et al. Metastatic pattern of malignant melanoma: A study of 216 autopsy cases. *Am J Surg*. 1978; 135(6):807-810

Paul WE. Dendritic cells bask in the limelight. *Cell*. 2007;130(6):967-970.

Pedoeem A, Azoulay-Alfaguter I, Strazza M, Silverman GJ, Mor A. Programmed death-1 pathway in cancer and autoimmunity. *Clin Immunol*. 2014;153(1):145-152.

Pembrolizumab Investigator's Brochure. Merck & Co., Inc., Whitehouse Station, NJ, USA.

Pena-Cruz V, McDonough SM, Diaz-Griffero F, Crum CP, Carrasco RD, Freeman GJ. PD-1 on immature and PD-1 ligands on migratory human Langerhans cells regulate antigen-presenting cell activity. *J Invest Dermatol*. 2010;130(9):2222-2230.

Pilon-Thomas S, Mackay A, Vohra N, Mule JJ. Blockade of programmed death ligand 1 enhances the therapeutic efficacy of combination immunotherapy against melanoma. *J Immunol*. 2010;184(7):3442-3449.

Preston CC, Maurer MJ, Oberg AL, Visscher DW, Kalli KR, Hartmann LC, et al. The ratios of CD8+ T cells to CD4+CD25+ FOXP3+ and FOXP3- T cells correlate with poor clinical outcome in human serous ovarian cancer. *PLoS One*. 2013;8(11):e80063.

Puzanov I, Milhem M, Andtbacka R, et al. Survival, safety, and response patterns in a phase 1b multicenter trial of talimogene laherparepvec (T-VEC) and ipilimumab (ipi) in previously untreated, unresected stage IIIB-IV melanoma. *J Clin Oncol.* 2015;33 (suppl; abstr 9063).

Puzanov I, Milhem MM, Andtbacka RHI, et al. Primary analysis of a phase Ib multicenter trial to evaluate safety and efficacy of talimogene laherparepvec (T-VEC) and ipilimumab (ipi) in previously untreated, unresected stage IIIB-IV melanoma. *J Clin Oncol*. 2014;32:5s.

Salgado R, Denkert C, Demaria S, et al. Harmonization of the evaluation of tumor infiltrating lymphocytes (TILs) in breast cancer: recommendations by an international TILs-working group 2014. *Ann Oncol*. 2014.

Sanmamed MF, Chen L. Inducible expression of B7-H1 (PD-L1) and its selective role in tumor site immune modulation. *Cancer J*. 2014;20(4):256-261.

Schatton T, Scolyer RA, Thompson JF, Mihm MC Jr. Tumor-infiltrating lymphocytes and their significance in melanoma prognosis. *Methods Mol Biol*. 2014;1102:287-324.

Schreiber RD, Old LJ, Smyth MJ. Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. *Science*. 2011;331(6024):1565-1570.

Sheppard KA, Fitz LJ, Lee JM, Benander C, George JA, Wooters J, et al. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. *FEBS Lett*. 2004;574(1-3):37-41.

Shirabe K, Motomura T, Muto J, Toshima T, Matono R, Mano Y, et al. Tumor-infiltrating lymphocytes and hepatocellular carcinoma: pathology and clinical management. *Int J Clin Oncol*. 2010;15(6):552-558.

Spranger S, Koblish HK, Horton B, Scherle PA, Newton R, Gajewski TF. Mechanism of tumor rejection with doublets of CTLA-4, PD-1/PD-L1, or IDO blockade involves restored IL-2 production and proliferation of CD8(+) T cells directly within the tumor microenvironment. *J Immunother Cancer*. 2014;2:3.

Strome SE, Dong H, Tamura H, Voss SG, Flies DB, Tamada K, et al. B7-H1 blockade augments adoptive T-cell immunotherapy for squamous cell carcinoma. *Cancer Res*. 2003;63(19):6501-6505.

Talimogene Laherparepvec Investigator's Brochure. Amgen Inc, Thousand Oaks, CA, USA.

Talmadge JE. Immune cell infiltration of primary and metastatic lesions: mechanisms and clinical impact. *Semin Cancer Biol*. 2011;21(2):131-138.

Taube JM, Anders RA, Young GD, Xu H, Sharma R, McMiller TL, et al. Colocalization of inflammatory response with B7-h1 expression in human melanocytic lesions supports an adaptive resistance mechanism of immune escape. *Sci Transl Med*. 2012;4(127):127-137.

Topalian SL, Drake CG, Pardoll DM. Targeting the PD-1/B7-H1(PD-L1) pathway to activate anti-tumor immunity. *Curr Opin Immunol*. 2012;24(2):207-212.

Transgene. Global Partners SillaJen, Transgene and Lee's Pharmaceutical Confirm Clinical Development Plan for Pexa-Vec. News Release, Busan, South Korea; San Francisco, CA, USA; Strasbourg, France and Hong Kong, March 26, 2014. http://www.transgene.fr

Transgene. Transgene Reports 2013 Half Year Results. News Release, Stausbourg, France, September 12, 2013. http://www.transgene.fr

United States National Institutes of Health. Hepatocellular Carcinoma Study Comparing Vaccinia Virus Based Immunotherapy Plus Sorafenib vs Sorafenib Alone (PHOCUS [NCT02562755]). December 2016. https://clinicaltrials.gov/ct2/show/record/NCT02562755. Accessed 03 March, 2017.

Uppaluri R, Dunn GP, Lewis JS Jr. Focus on TILs: prognostic significance of tumor infiltrating lymphocytes in head and neck cancers. *Cancer Immun*. 2008;8:16.

Weber J. Immune checkpoint proteins: a new therapeutic paradigm for cancer--preclinical background: CTLA-4 and PD-1 blockade. *Semin Oncol*. 2010;37(5):430-439.

Wolff AC, Hammond ME, Schwartz JN, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. *J Clin Oncol*. 2007;25(1):118-245.

Yao S, Chen L. PD-1 as an immune modulatory receptor. *Cancer J*. 2014;20(4):262-264.

Yoon HH, Orrock JM, Foster NR, Sargent DJ, Smyrk TC, Sinicrope FA. Prognostic impact of FoxP3+ regulatory T cells in relation to CD8+ T lymphocyte density in human colon carcinomas. *PLoS One*. 2012;7(8):e42274.

Zhang L, Gajewski TF, Kline J. PD-1/PD-L1 interactions inhibit antitumor immune responses in a murine acute myeloid leukemia model. *Blood*. 2009;114(8):1545-1552.

Zhang X, Schwartz JC, Guo X, Bhatia S, Cao E, Lorenz M, et al. Structural and functional analysis of the costimulatory receptor programmed death-1. *Immunity*. 2004;20(3):337-347.

Zhu AX, Finn RS, Edeline J, et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. *Lancet Oncol.* 2018;19(7):940-952.

Zhu AX, Kang YK, Yen CJ, et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased alpha-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2019;20(2):282-296.

14. APPENDICES

Appendix A. Additional Safety Assessment Information

Adverse Event Grading Scale

The Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 is available at the following location:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Appendix B. Sample Electronic Serious Adverse Event Contingency Report Form (paper-based 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.

FORM-066006 *Instructions Page 1 of 2* *Version 7.0 Effective Date: 1 February 2016*

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.

Protocol specified hospitalizations are exempt.

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.*

A Study # 20140318 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 c[illegible]his study

FAX #

<<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	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; 06 Congenital anomaly / birth defect; 08 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 #

A Study # 20140318 Talimogene Laherparepvec	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

								☐ Unavailable / Unknown

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

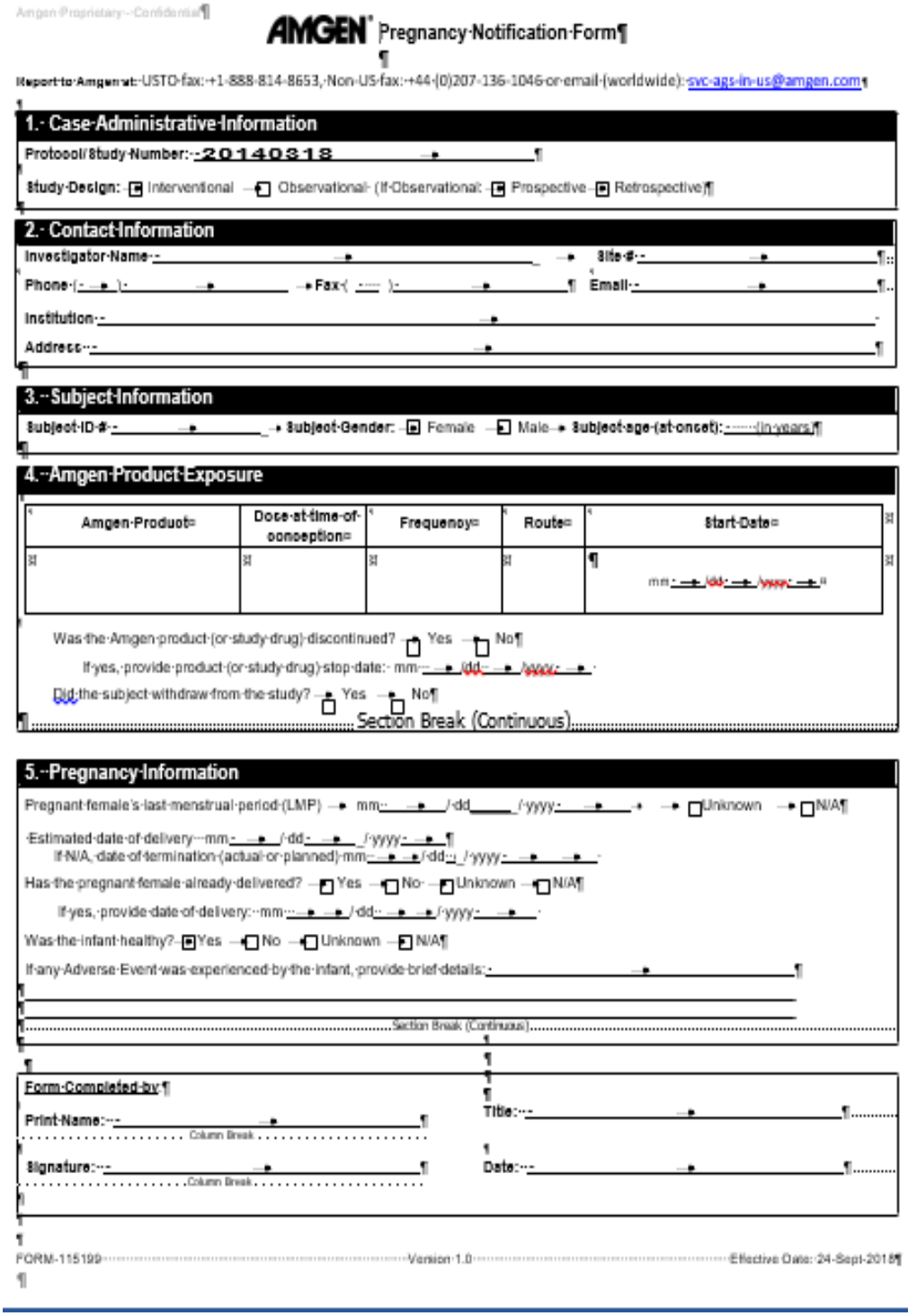
A Study # 20140318 Talimogene Laherparepvec	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

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 -	Title	Date
_____ *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.*		

Appendix C. Pregnancy and Lactation Notification Forms



Amgen Proprietary – Confidential

AMGEN Pregnancy Notification Form

Report to Amgen at: US TO 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: 20140318

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

Section Break (Continuous)

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: _____

Section Break (Continuous)

Form Completed by

Print Name: _____ Title: _____

Column Break

Signature: _____ Date: _____

Column Break

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: 20140318

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 irRC-RECIST Guidelines for Assessment of Disease Response

Note: Immune-related Response Criteria (irRC) simulating Response Evaluation Criteria in Solid Tumors version (RECIST) version 1.1 [irRC-RECIST] defined by Nishino et al, 2014, with modification will employed to account for unique tumor response characteristics observed with immunotherapies to enable treatment beyond progression, if the subject is clinically stable.

Method of Measurement Tumor Lesions:

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. Scan slices should ideally be 3 to 5 mm. 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 (IV) 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 IV and oral contrast) then the CT portion of the PET/CT can be used for tumor measurements.

Ultrasound:

Ultrasound (US) should not be used as a primary method to assess liver lesion measurements in response to treatment. If new lesions are identified by US in the course of the study, confirmation by CT or MRI is advised.

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.

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 Lesions:

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 that were not chosen as target lesions. Only cancerous lesions should be selected as non-measurable lesions and not indeterminate lesions and lesions that could be cancer. 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.

Fluid Collections

Ascites, pleural effusion, or pericardial effusion should not be selected as non-measurable disease at baseline or, if new or increased, as evidence of progressive disease (PD). These collections may occur with both benign and malignant conditions, and their etiology is often not clear. These collections may often be removed via

interventional procedures, which can lead to a false interpretation of disease response. Thus, these fluid collections should not be used as a baseline non-target or as evidence of disease response.

*** 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.
- Osteolytic (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.
- Many osteoblastic (blastic) bone abnormalities can be benign and should not be selected as baseline lesions. An isolated new small blastic lesion should not be selected as a new lesion unless there is demonstrated growth on subsequent scans. Multiple new blastic lesions that are clearly cancerous may be considered for new 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 cystic lesion is clearly cancerous and has both cystic and solid components, then the complete lesion should be measured including both components without excluding the cystic portion of a cystic tumor lesion when measuring.

Lesions with Prior Local Treatment:

Tumor lesions situated in a previously irradiated area, or an area subject to other loco-regional therapy, should not be 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.

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. In situations where larger lesions cannot be accurately measured repeatedly (eg, near the diaphragm where respiratory changes may affect measurements), smaller lesions that meet criteria for measurability may be selected instead.

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 and pathological lymph node with short axis ≥ 10 mm but < 15 mm, should be identified as non-target lesions. Measurable non-target lesions (ie, lesions in an organ beyond the allowed maximum number of targets that would otherwise qualify as target lesions) should also be recorded and assessed qualitatively over the course of therapy. Non-measurable non-target disease measurements are not required, but these lesions are evaluated at each timepoint and will be evaluated as 'present', 'absent', or in rare cases 'unequivocal progression'. If a significant partial response (PR) is observed in a non-target lesion, it should be described as a comment.

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 (ie, accurately and serially measured in at least 2 dimensions and for which the longest diameter is ≥ 10 mm for non-nodal lesions or the short axis is ≥ 15 mm for non-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 single timepoint, 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, the additional lesions would be considered new non-measurable lesions.

Tumor Burden = sum of diameters 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 radiographically assessed non-nodal disease the convention will be used that if a lesion being measured decreases in size to ≤ 5 mm in diameter or if it is believed to be present and faintly seen but too small to measure, a value of 5 mm will be assigned. If the non-nodal lesion subsequently increases in size to greater than or equal to 5 mm in one dimension, its true size will be recorded. 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 complete response (CR), each node must achieve a short axis <10 mm.

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), and, in the case of CR, 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 19 and Table 20.

Table 19. Definition of Measurable Tumor Response (Baseline Target and New, Measurable Lesions)

Complete Response (CR):	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 (PR):	Decrease in tumor burden* ≥ 30% relative to baseline confirmed by a consecutive assessment at least 4 weeks (28 days) after first documentation
Progressive Disease (PD):	Increase in tumor burden* ≥ 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 PD.
Stable Disease (SD):	Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD.
Unable to Evaluate (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. Note: If a subset of target / new measurable lesions were assessed and the tumor burden increase of the subset is sufficient to declare PD without the contribution of the unevaluated lesions, then PD should be reported.
Not Applicable (NA)	No target lesions were identified at baseline
Not Done (ND)	Radiographic imaging or clinical assessment was not performed at this time point to evaluate the response of measurable lesions

* Tumor Burden = sum of diameters of target lesions + sum of diameter of new, measurable lesions.
Diameters used:

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

Table 20. 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, nonmeasurable lesions	Using irRC-RECIST
↓100[e]	Absent/NA[d]	Absent	CR[b]
↓100	Stable/ND	Any	PR[b]
↓100	Unequivocal progression	Any	PR[b]
↓≥ 30	Absent/Stable/ND/NA[d]	Any	PR[b]
↓≥ 30	Unequivocal progression	Any	PR[b]
↓< 30 to ↑< 20	Absent/Stable/ND/NA[d]	Any	SD
↓< 30 to ↑< 20	Unequivocal progression	Any	SD
↑≥ 20[f]	Any	Any	PD[b]
UE	Any	Any	UE
ND	Any	Any	UE
NA[c]	Any	Any	UE

[a] Decrease disease relative to baseline, including new measurable lesions only (> 10 mm).
[b] Assuming response (CR or PR) or progression are confirmed by a second, consecutive assessment at least 4 weeks (28 days) apart.
[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 CR 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 PD.

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; UE = unable to evaluate; ND = not done; NA = not applicable.Determination of best overall response 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 stable disease (SD) even if new lesions were present, as long as they met the respective thresholds of response as described in Table 20.

Subjects with SD, particularly those with slow-declining tumor burden ≥ 20% from baseline at the last tumor assessment, are considered clinically meaningful because they show an objectively measurable reduction in tumor burden without reaching the 30% threshold that defines PR.

A best overall response of SD requires a visit response of SD or better no earlier than 77 days after the first dose date; otherwise the overall response will be UE.

Confirmation of Response (CR or PR):

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 (ie, biopsy) to confirm the CR status.

Confirmation of Disease Progression:

If a subject is classified as having PD at a postbaseline tumor assessment, then confirmation of PD by a second assessment ≥ 4 weeks (28 days) later in the absence of rapid clinical deterioration (ie, rapid decline in performance status) or symptomatic disease requiring rapid initiation of alternative systemic anti-cancer therapy is required. The definition of confirmation of progression represents a ≥ 20% and at least 5 mm absolute 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) 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 PD). It is recommended that this be done at the discretion of the investigator because follow-up with observation alone may not be appropriate for subjects with a rapid decline in performance status. Confirmation of PD allows for the capture of all observed responses using the irRC-RECIST as most of these late responding subjects have a trend toward response within 4 weeks (28 days) after initial PD.

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 specified. Every effort should be made to document the objective progression even after discontinuation of treatment.

Determining a New Nadir After Intervention-therapy:

After the intervention-therapy for liver lesions is completed, subjects will undergo radiological imaging by either CT or MRI or US according to the schedule defined in Section 7 of the protocol. The first post intervention tumor assessment will provide the “new nadir” from which progression will be assessed. Any remaining sites of disease

must continue to be followed as target and non-target lesions as designated at study screening. Post intervention tumor assessment will be performed until confirmed PD, according to the schedule of the study protocol.

Subjects who have had Complete Removal of the Lesion will be Evaluated as Follows:

The completely resected lesion should continue to be documented on the case report forms (CRFs) and assigned a default code of absent (for nontarget lesions) or a value of 0 mm for the longest diameter for the purpose of calculating the sum of the diameters (for target lesion), and determining the post intervention-therapy response. This will allow continued response determination from screening.

If the resected lesion contained no tumor 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 tumor 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.

Guidance on quantitative/qualitative reporting of fully resected lymph nodes is below (see Table 21).

If new radiographic imaging findings develop at the surgical/treatment site that were not present on the immediate post intervention-therapy imaging assessments and are indicative of tumor recurrence, the tumor will be considered a new lesion, and measured accordingly, with the response assessed as PD if increase in tumor burden $\geq$ 20% and at least 5 mm absolute increase relative to nadir compared with the first post intervention-therapy nadir at two time points at least 4 weeks (28 days) apart.

Table 21. Quantitative/Qualitative Reporting of Fully Resected Lymph Nodes

Lymph Node Type/Presence	Contained Cancer Under Pathology Evaluation?	Quantitative/qualitative Reporting
Target lymph node previously present	Yes/Unknown	If measurement available: Actual short axis
		If measurement not available: 10 mm short axis
	No	If measurement available: Actual short axis
		If measurement not available: 9 mm short axis
Non-target lymph node previously present	Yes/Unknown	Present
	No	Absent
Lymph node not previously present	Yes/Unknown	If measurement available and short axis < 15 mm: New non-measurable lymph node[a]
		If measurement available and short axis ≥ 15 mm: please enter actual measurements (do not default to 10 mm)[a]
		If measurement not available: New non-measurable lymph node[a]
	No	Not to be recorded as target or non-target lesion. Instead to be reported on Procedures electronic CRF.

[a] The initial dimension of a new measurable lymph node or presence of a new non-measurable lymph node should be reported at all subsequent assessments.

Subjects who have had Partial Removal/ Reduction of the Lesion will be Evaluated as Follows:

In subjects where the tumor can still be confidently identified, it should be measured (target lesion) or qualitatively evaluated (nontarget lesion) and response (CR, PR or SD) or progression should be determined. Response is judged compared to the screening time point and PD should be judged compared with the nadir as detailed in Table 19 and Table 20.

In subjects where the interventional-therapy was not thought to be completely effective and residual tumor cannot be distinguished from the effects of therapy, the size of the residual tumor should be considered too small to measure and assigned a default code of present (for nontarget lesion) or a default value of 5 mm as the sum of the diameters (for target lesion). If this is the nadir, PD will be judged from this sum of the diameters.

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

tumor 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 tumor 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.

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.

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 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.

Appendix E. Drug-induced Liver Injury Reporting and Additional Assessment

Reporting

To facilitate appropriate monitoring for signals of drug induced liver injury (DILI), cases of concurrent aspartate aminotransferase (AST) or alanine aminotransferase (ALT) and total bilirubin (TBL) and/or international normalization ratio (INR) elevation according to the criteria specified in Section 6.4, require the following:

- The event is to be reported to Amgen as a serious adverse event within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate CRF (eg, events CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to Amgen

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for serious adverse events defined in Section 9.1.2.

Additional Clinical Assessments and Observation

All subjects in whom investigational product is withheld (either permanently or conditionally) due to potential DILI as specified in Section 6.4 are to undergo a period of "close observation" until abnormalities return to normal or to the subject's baseline levels. Assessments that are to be performed during this period include:

- Repeat AST, ALT, ALP, bilirubin (total and direct), and INR within 24 hours
- In cases of TBL $>$ 2x upper limit of normal (ULN) or INR $>$ 1.5, retesting of liver tests, bilirubin (total and direct), and INR is to be performed every 24 hours until laboratory abnormalities improve

Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize or the investigational product(s) or protocol-required therapies has/have been discontinued AND the subject is asymptomatic

- Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL:

  Obtain complete blood count with differential to assess for eosinophilia

  Obtain serum total immunoglobulin G (IgG), anti-nuclear antibody, anti-smooth muscle antibody, and liver kidney microsomal antibody 1 to assess for autoimmune hepatitis

  Obtain serum acetaminophen (paracetamol) levels

  Obtain a more detailed history of:

  Prior and/or concurrent diseases or illness

  Exposure to environmental and/or industrial chemical agents

Symptoms (if applicable) including right upper quadrant pain, hypersensitivity type reactions, fatigue, nausea, vomiting and fever

Prior and/or concurrent use of alcohol, recreational drugs and special diets

Concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms

Obtain viral serologies

Obtain creatinine phosphokinase, haptoglobin, lactate dehydrogenase (LDH), and peripheral blood smear

Perform appropriate liver imaging if clinically indicated

- Obtain appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- Obtain hepatology consult (liver biopsy may be considered in consultation with an hepatologist)
- Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal. The “close observation period” is to continue for a minimum of 4 weeks after discontinuation of investigational product.

The potential DILI event and additional information such as medical history, concomitant medications and laboratory results must be captured in corresponding CRFs.

Appendix F. Child-Pugh Score

Measure	1 point	2 points	3 points
Total bilirubin, µmol/l (mg/dl)	< 34 (< 2)	34-50 (2-3)	> 50 (> 3)
Serum albumin, g/dl	> 3.5	2.8-3.5	< 2.8
INR/PT	< 1.7/4.0	1.7-2.3/4.0-6.0	> 2.3/6.0
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade 1 to 2 (or suppressed with medication)	Grade 3 to 4 (or refractory)

Points	Class
5 to 6	A
7 to 9	B
10 to15	C

References:

Child CG, Turcotte JG. Surgery and portal hypertension. *Major Prob Clin Surg*. 1964;1:1-85.

Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, William R. Transection of the oesophagus for bleeding oesophageal varices. *The Br J Surg.* 1973;60(8):646-649.

Appendix G. Eastern Cooperative Oncology Group Performance Status Scale

Grade	Description
0	Fully active, able to carry on all predisease 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 H. Contraceptive Guidance and Collection of Pregnancy and Lactation Information For Talimogene Laherparepvec

Study-specific contraception requirements for female of childbearing potential are outlined in Section 4.1.2.

Female subjects of childbearing potential must receive pregnancy prevention counseling and be advised of the risk to the fetus if they become pregnant during treatment and after the last dose of protocol-required therapies.

Additional medications given during the study may alter the contraceptive requirements. These additional medications may require female subjects to use highly effective methods of contraception and for an increased length of time. In addition, male subjects may also be required to use contraception. The investigator must discuss these contraceptive changes with the subject.

Definition of Females of Childbearing Potential

A female is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Females in the following categories are not considered female of childbearing potential:

Premenopausal female with 1 of the following:

- Documented hysterectomy;
- Documented bilateral salpingectomy; or
- Documented bilateral oophorectomy.

Note: Site personnel documentation from the following sources is acceptable:
1) review of subject's medical records; 2) subject's medical examination; or
3) subject's medical history interview.

Premenarchal female

Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Acceptable Methods of Effective Contraception

- Combined (estrogen and progestogen containing) or progestogen-only hormonal methods given via oral, intravaginal, transdermal, injectable, or implantable route)
- Intrauterine device (IUD)
- Intrauterine hormonal-releasing system (IUS)
- Bilateral tubal ligation/occlusion
- Vasectomized partner (provided that partner is the sole sexual partner of the female subject of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success)
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments; the reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject)
- Double barrier method: the male uses a condom and the female may choose either a cap, diaphragm, or sponge with spermicide (a female condom is not an option due to the risk of tearing when both partners use a condom)

Unacceptable Methods of Birth Control for Female Subjects

Birth control methods that are considered unacceptable in clinical trials include:

- Periodic abstinence (calendar, symptothermal, postovulation methods)
- Withdrawal (coitus interruptus)
- Spermicides only
- Lactational amenorrhoea method

Appendix I. Contraceptive Guidance and Collection of Pregnancy and Lactation Information 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 224, 225, and 226) from the day of pembrolizumab initiation (or 14 days prior to the initiation of pembrolizumab for oral contraception) throughout the study period up to 4 months (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.

Use of Pembrolizumab in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with systemic pembrolizumab, the subject will immediately be removed from the study. The outcome of the pregnancy will be reported to the sponsor and followed as described in Section 9.3 (Pregnancy and Lactation Reporting). If a male subject impregnates his female partner, the investigator must be informed immediately and the pregnancy reported to the sponsor and followed as described in Section 9.3 (Pregnancy and Lactation Reporting).

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.

Amendment 6

Protocol Title: A Phase 1b/2, Multicenter, Open-label, Basket Trial to Evaluate the Safety of Talimogene Laherparepvec Injected into Liver Tumors Alone and in Combination With Systemic Pembrolizumab in Phase 1b and to Evaluate the Efficacy and Safety of Intratumoral Talimogene Laherparepvec in Combination With Systemic Pembrolizumab to Treat Subjects With Advanced Solid Tumors in Phase 2 (MASTERKEY-318)

Amgen Protocol Number (Talimogene Laherparepvec 20140318)

EudraCT number: 2014-005386-67

NCT number: NCT02509507

Amendment Date: 26 October 2021

Rationale:

This protocol is being amended to stop study-related hepatic biopsies and hepatic injections of talimogene laherparepvec based on the overall safety assessment of the hepatic hemorrhage signal following two serious adverse events of hepatic haemorrhage that resulted in death in the study. While the full safety assessment results did not suggest an increased risk of hepatic haemorrhage with talimogene laherparepvec as a medication, there is a potential risk of hepatic haemorrhage with the transcutaneous intrahepatic route of administration of talimogene laherparepvec and hepatic biopsies. As a result, the protocol is amended to remove these procedures from study conduct. Additionally, the final enrollment numbers have been updated in the protocol as enrollment has stopped for this study.

Amendment 5

Protocol Title: A Phase 1b/2, Multicenter, Open-label, Basket Trial to Evaluate the Safety of Talimogene Laherparepvec Injected into Liver Tumors Alone and in Combination With Systemic Pembrolizumab in Phase 1b and to Evaluate the Efficacy and Safety of Intratumoral Talimogene Laherparepvec in Combination With Systemic Pembrolizumab to Treat Subjects With Advanced Solid Tumors in Phase 2 (MASTERKEY 318)

Amgen Protocol Number 20140318

EudraCT number: 2014-005386-67

NCT number: NCT02509507

Amendment Date: 02 July 2021

Rationale:

This protocol amendment dated 02 July 2021 is being amended to:

- fix the minor discrepancies and inconsistencies within the protocol
  - removed 'Swab of Injection Site Surfaces and Occlusive Dressings' at Week 10 from the table 12 to maintain consistency with footnotes
  - corrected number of days (missing in brackets) in footnote 't' of table 13 for the samples collected post 14 days after talimogene laherparepvec administration for all subjects at week 1 and 4
  - updated time points for specialized/central laboratory tests and tumor biopsy procedures in the section 7.2.2 to maintain consistency with footnotes of table 13
- clarified medical monitor approval requirements for continuing talimogene in Part 1 and Part 2 (section 3.1.3)
- updated exclusion criteria 207 to separate pneumonitis into standalone criteria 238
- removed the exclusion of prior checkpoint inhibitors for basal cell carcinoma (BCC) patients to reflect the approval of cemiplimab in this population
- updated Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated With Pembrolizumab
- updated an exception considered to continue treatment beyond progression (Section 6.6)
- updated the requirement to report fatal disease related events (DREs) as serious adverse events (SAEs)
- clarified the interim safety analysis language in Part 2 (Section 10.3.1.2)

- updates SAE reporting forms
- updated pregnancy and lactation notification forms
- clarified primary and final analyses clinical study report (CSR) plans
- aligned the protocol with current Amgen protocol template and safety reporting language
- typographical, formatting, and editorial changes were done throughout the protocol

Amendment 4

Protocol Title: A Phase 1b/2, Multicenter, Open-label, Basket Trial to Evaluate the Safety of Talimogene Laherparepvec Injected into Liver Tumors Alone and in Combination With Systemic Pembrolizumab in Phase 1b and to Evaluate the Efficacy and Safety of Intratumoral Talimogene Laherparepvec in Combination With Systemic Pembrolizumab to Treat Subjects With Advanced Solid Tumors in Phase 2 (MASTERKEY-318)

Amgen Protocol Number 20140318

EudraCT number: 2014-005386-67

NCT number: NCT02509507

Amendment Date: 30 June 2020

Rationale:

This protocol is being amended to:

- Remove the 6 hour observation period and associated assessments for Part 2 subjects not receiving intrahepatic injections
- Only include Part 2 enrolled subjects as part of the efficacy futility analyses
- Combine study Arms VI and VII
- Make updates to collection time points of cytokines and quantitative polymerase chain reaction (qPCR)
- Decrease sample size from 244 to 206
- Clarify inclusion criterion for triple negative breast cancer subjects (inclusion criterion 114)
- Update administrative edits

Amendment 3

Protocol Title: A Phase 1b/2, Multicenter, Open-label, Basket Trial to Evaluate the Safety of Talimogene Laherparepvec Injected into Liver Tumors Alone and in Combination With Systemic Pembrolizumab in Phase 1b and to Evaluate the Efficacy and Safety of Intratumoral Talimogene Laherparepvec in Combination With Systemic Pembrolizumab to Treat Subjects With Advanced Solid Tumors in Phase 2 (MASTERKEY-318)

Amgen Protocol Number 20140318

EudraCT number: 2014-005386-67

NCT number: NCT02509507

Amendment Date: 21 October 2019

Rationale:

- This protocol is being amended to:
  - Update study title to reflect phase and type of study, combination therapy, and to indicate primary purpose of Phases 1b and 2
  - Allow intratumoral injection of talimogene laherparepvec into cutaneous, subcutaneous, and liver lesions and involved lymph nodes in Part 2 of the study, as safety of intrahepatic injection of talimogene laherparepvec in combination with systemic pembrolizumab will be established in Part 1. Intrahepatic injection is not required in Part 2, but it is allowed if there are injectable liver lesions
  - Clarify that liver injection is not a requirement or priority in Part 2
  - Expand allowable injectable disease to include subcutaneous and cutaneous tumor lesions and involved lymph nodes
  - Change the tumor types in Part 2 to the following non-HCC tumor types to reflect the expanded allowable injection sites: hormone receptor positive breast adenocarcinoma [BC], triple negative breast cancer [TNBC], colorectal adenocarcinoma [CRC], cutaneous squamous cell carcinoma (CSCC), basal cell carcinoma (BCC)
  - Create additional BC cohort to include separate cohorts for triple negative breast cancer (TNBC) and hormone receptor positive subjects
  - Create additional hepatocellular carcinoma (HCC) cohort to include separate cohorts for HCC subjects with and without viral hepatitis
  - Allow for well controlled viral hepatitis and allow antiviral therapy for hepatitis in new cohort 6B for HCC in Part 1 and Arm VI in Part 2 of the study
  - Change the sample size in Part 1 and Part 2 to reflect the number of cohorts/arms now under study
  - Update the study schema to reflect new cohort in Part 1 and new tumor types in Part 2
  - Update the eligibility criteria based on new cohorts and revised tumor types

- Shorten 23 hour observation window to 6 hours in Part 2, after review of safety data from monotherapy and combination cohorts enrolled to date in Part 1
- Add collection of Patch 1 (PTCH) mutation status in BCC cohort if available
- Add collection of BRCA1 and 2 mutation status in BC cohort if available
- Add optional liver ultrasound to schedule of assessments for monotherapy and combination cohorts enrolled to date in Part 1 and combination cohorts Part 2.
- Remove 24 hour and 48 hour timepoints in Week 1 and Week 4 from Part 2 schedule of assessments, after review of available data from Part 1
- Remove assessments for anti-pembrolizumab antibodies, and pembrolizumab pharmacokinetics (PK) in Part 2
- Remove blood, urine, and swab collection at 24, and 48 hours in Part 2, after review of available data from Part 1
- Allow continuation of talimogene laherparepvec after cycle 12 in Part 2 if in the opinion of the investigator, the subject is deriving clinical benefit from the study regimen, the subject is still receiving pembrolizumab, and the investigator obtains approval from the sponsor medical monitor
- Clarify that subjects can receive a maximum of 12 cycles of talimogene laherparepvec in Part 1 and 35 cycles in Part 2
- Allow resumption of talimogene laherparepvec at progression if previously discontinued
- Allow up to 8 mL of talimogene laherparepvec to be used in Part 2 if 8 mL is shown safe in either Group A or B in Part 1
- Add clinical tumor assessments in Part 2
- Create a separate schedule of assessment table for Part 2 to reflect the changes to cohort, tumor types, and time points
- Revise the list of laboratory analytes to align with new tumor types
- Add language regarding events of clinical interest specifically for Group B HCC subjects
- Add disease related events (DRE) language that instructs sites to transmit serious DREs in the same manner that they transmit serious adverse events and with the same timeline expectations
- Remove language on self-evident corrections from the protocol to be consistent with current regulations
- Update HCC data in the Background and Rationale section to reflect new available clinical data since the last amendment
- Update CTCAE version to 4.03
- Update references to reflect added information in the Background and Rationale section
- Make editorial and administrative changes for grammatical reasons as well as for internal consistency within the protocol

Amendment 2

Protocol Title: A Phase 1b/2, Multicenter, Open-label Trial to Evaluate the Safety of Talimogene Laherparepvec Injected Into Liver Tumors Alone and in Combination With Systemic Pembrolizumab (MASTERKEY-318)

Amgen Protocol Number Talimogene Laherparepvec 20140318

EudraCT number 2014-005386-67

NCT number NCT02509507

Amendment 2 Date: 18 October 2017

Rationale:

This amendment was revised to:

- Add a collaborator drug, pembrolizumab, from Merck. This resulted in:
  - Adding combination cohorts (talimogene laherparepvec and pembrolizumab) in Part 1 of the study
  - The opening on Group B will now be independent of Group A safety results
  - Phase of study changed to 1b/2
  - Changing Part 2 of the study to include combination cohorts only
  - Pembrolizumab-specific requirements added to the protocol
- Align with more recent protocol template text:
  - Section 9 (Safety Data Collection, Recording, and Reporting)
  - Updated the pregnancy and lactation reporting forms
  - Added contraception, pregnancy, and lactation information to Appendix H and Appendix I
  - Section 12.6 (Publication Policy)
- Editorial changes (ie, typographic, grammatical, and formatting errors) and abbreviation corrections were made throughout the protocol in accordance with Amgen Inc. Style Guide.

Amendment 1

Protocol Title: A Phase 1, Multicenter, Open-label Trial to Evaluate the Safety of Talimogene Laherparepvec Injected into Liver Tumors

Amgen Protocol Number TVEC 20140318

EudraCT number 2014-005386-67

Amendment Date: 26 April 2016

Rationale:

The previous version of the protocol considered a grade 3 or higher non-hematologic laboratory value that persisted for > 1 week as meeting the criteria for a DLT, even if the abnormal laboratory value did not result in a medical intervention or hospitalization. This criterion could result in dose limiting toxicities (DLTs) being determined for abnormal laboratory values that were not clinically important. To date, 1 subject has had a grade 3 or higher gamma-glutamyl transferase (GGT) elevation that persisted for over 1 week, which was considered related to talimogene laherparepvec, and was subsequently defined as a DLT under the original protocol. The subject was asymptomatic, and the GGT elevation was considered to not be of any clinical significance. In order to prevent abnormal laboratory values that are not clinically significant from being classified as DLTs, the Dose Level Review Team (DLRT) decided that the protocol should be amended. This modification will also be consistent with the protocol language in Section 9.2.2, where abnormal laboratory findings without clinical significance (based on investigator's judgement) are not to be recorded as adverse events.

The following key changes have been incorporated into protocol amendment 1:

- The criteria for grade 3 or higher non-hematologic laboratory values that define DLT have been changed so that those that persist for > 1 week which are deemed not clinically important by both the investigator and sponsor do not trigger a DLT. Any grade 3 or higher non-hematologic laboratory value will still be considered a DLT if medical intervention is required or if it leads to hospitalization.
- Treatment can continue for grade 3 or higher non-hematologic laboratory values that persist for > 1 week and are deemed not clinically important by both the investigator and sponsor so that subjects can continue study treatment in spite of persistently elevated non-hematologic laboratory values with no clinical significance and long half-lives such as GGT.
- Added hepatitis D viral RNA as another acceptable method of testing as some institutions do not use hepatitis D serology testing.

- The irRC-RECIST criteria definition has been edited to make it more consistent with the conventional RECIST criteria and irRC simulating RECIST as described by Nishino et al.
- Clarified certain laboratory tests and timing of study procedures.
- Other minor changes include:
- Administration and editorial corrections
- Updating adverse event and disease related event language to clarify definitions and reporting periods
- Specifying time points for liver tumor biopsies