Title: A Phase 1b Study of Talimogene Laherparepvec in Combination With Atezolizumab in Subjects With Triple Negative Breast Cancer and Colorectal Cancer With Liver Metastases

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Confidentiality Notice

Investigator's Agreement

I have read the attached protocol entitled: A Phase 1b Study of Talimogene Laherparepvec in Combination With Atezolizumab in Subjects With Triple Negative Breast Cancer and Colorectal Cancer With Liver Metastases, dated **08 July 2019**, 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 Study of Talimogene Laherparepvec in Combination With Atezolizumab in Subjects With Triple Negative Breast Cancer and Colorectal Cancer With Liver Metastases

Study Phase: Phase 1b

Indication: Triple negative breast cancer and colorectal cancer with liver metastases

Primary Objective:

To evaluate the safety, as assessed by incidence of dose limiting toxicities (DLTs), of intrahepatic injection of talimogene laherparepvec into liver metastases in combination with intravenously administered atezolizumab separately in subjects with triple negative breast cancer and colorectal cancer

Secondary Objectives:

To evaluate the efficacy of talimogene laherparepvec in combination with atezolizumab separately in subjects with triple negative breast cancer and colorectal cancer with liver metastases as assessed by:

- Objective response rate (ORR), best overall response (BOR), duration of response (DOR), lesion level responses in injected and uninjected tumor lesions (overall, hepatic, nonhepatic) disease control rate (DCR), durable response rate (DRR), progression-free survival (PFS), overall survival (OS) by cohort (triple negative breast cancer and colorectal cancer)

Safety Objective:

- To evaluate the safety and tolerability of intrahepatic injection of talimogene laherparepvec into liver metastases in combination with intravenously administered atezolizumab separately in subjects with triple negative breast cancer and colorectal cancer

Hypotheses:

It is hypothesized that intrahepatic injection of talimogene laherparepvec in combination with intravenously administered atezolizumab in subjects with triple negative breast cancer and colorectal cancer with liver metastases will be safe and well tolerated with a DLT rate ≤ 10%.

Primary Endpoint:

- Subject incidence of DLTs by cohort (triple negative breast cancer and colorectal cancer)

Secondary Endpoints:

- ORR, BOR, DOR, lesion level responses (≥ 30% and 100% decrease) in injected and uninjected tumor lesions (overall, hepatic, nonhepatic), DRR, DCR, PFS, and OS by cohort (triple negative breast cancer and colorectal cancer)

Safety Endpoint:

- Subject incidence of adverse events and clinically relevant laboratory abnormalities by tumor type (triple negative breast cancer and colorectal cancer)

Study Design: This is a phase 1b, multicenter, open-label study to evaluate the safety of intrahepatic injection of talimogene laherparepvec in combination with intravenously administered atezolizumab in subjects with triple negative breast cancer and colorectal cancer with liver metastases. Talimogene laherparepvec will be injected intrahepatically in combination with intravenous atezolizumab to approximately 36 **DLT-evaluable** subjects in 2 parallel cohorts. Cohort 1 will comprise subjects with triple negative breast cancer with liver metastases (n =18 **DLT-evaluable subjects**). Cohort 2 will comprise subjects with colorectal cancer with unresectable liver metastases (n =18 **DLT-evaluable subjects**). 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 atezolizumab and 3 weeks following the initial 10^8 PFU/mL dose of talimogene laherparepvec and atezolizumab or the start of cycle 3, whichever occurs first. DLTs will be

evaluated based on the first 18 DLT-evaluable subjects in each cohort separately. A Dose Level Review Team (DLRT) will review the safety data to evaluate possible drug effects and DLT. To be evaluable for a DLT, subjects must have had the opportunity to be on treatment for at least 2 cycles from the initial dose of study treatment and have received at least 2 doses of talimogene laherparepvec and 2 doses of atezolizumab in combination, or have a DLT during the DLT evaluation period. Subjects may be replaced if they are not evaluable for DLT in order to obtain 18 DLT-evaluable subjects. There will be a safety interim analysis after the first 4 to 6 DLT-evaluable subjects have been enrolled in this study and a safety analysis after 18 DLT-evaluable subjects have been enrolled in a cohort. Enrollment will be suspended during the first safety interim analysis. At the discretion of the DLRT, additional safety analyses may be conducted as warranted. Treatment will continue until a subject experiences a DLT (during the DLT evaluation period), has complete response (CR), has need for an alternative anticancer therapy, or experiences an adverse event necessitating drug discontinuation. In addition, treatment will be discontinued for talimogene laherparepvec if the subject has no injectable lesions, upon confirmed progressive disease (PD) per modified immune related response criteria Response Evaluation Criteria in Solid Tumors (irRC-RECIST) or rapid clinical deterioration. Atezolizumab will be discontinued upon symptomatic disease progression. All subjects will complete a safety follow-up visit approximately 30 (+ 7) days after the last dose of study treatment. After the safety follow-up visit, all subjects will enter the long-term follow-up. Subjects will be followed for survival, subsequent anticancer therapies and treatment-related adverse events every 12 weeks (± 28 days) for approximately 24 months after the last subject is enrolled.

Sample Size: Approximately 36 subjects will be enrolled (18 **DLT-evaluable** subjects in each cohort).

Summary of Subject Eligibility Criteria: To be eligible for the study subjects must be age ≥ 18 years and have a diagnosis of triple negative breast cancer or colorectal cancer with liver metastases. Subjects must have disease progression during or after ≥ 1 prior standard of care systemic anti-cancer therapy for metastatic disease. Subjects must have measurable liver lesions that are suitable for injection. Subjects must have Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, adequate organ function and life expectancy ≥ 5 months. Female subjects of childbearing potential must have a negative serum pregnancy test. Subjects will be excluded if they are candidates for hepatic surgery or locoregional therapy of liver metastases with curative intent, or if more than one-third of the liver is estimated to be involved with metastases or if they have macroscopic intravascular invasion into the main portal vein, hepatic vein, or vena cava. Subjects will not be eligible if they are receiving or have received liver metastatic-directed therapy (eg, radiation, ablation, embolization), hepatic surgery, antibody-based therapy, or immunotherapy < 4 weeks prior to enrollment. Subjects with a history of malignancy (other than the current malignancy) within the past 5 years will be excluded with some exceptions. Subjects with active or untreated central nervous system (CNS) metastases, presence of leptomeningeal disease or spinal cord compression will be excluded. Subjects with symptomatic autoimmune disease or who are immunosuppressed will be excluded. Subjects with active herpetic skin lesions or prior complications of herpetic infection (eg, herpetic keratitis or encephalitis), or who require intermittent and chronic systemic treatment with an antiherpetic drug (other than intermittent topical use), will not be eligible for the study. Subjects receiving concomitant treatment with warfarin are not eligible for the study.

For a full list of eligibility criteria, please refer to Section 4.1 and 4.2.

Investigational Products

Amgen Investigational Product Dosage and Administration: Talimogene laherparepvec will be manufactured and packaged by Amgen Inc. Talimogene laherparepvec is supplied as a sterile frozen liquid in a single-use vial. Each vial contains a minimum of 1.0 mL talimogene laherparepvec at either 10^6 plaque-forming unit (PFU)/mL or 10^8 PFU/mL concentrations. The first cycle of talimogene laherparepvec will be 21 (+ 3) days. Subsequent cycles of talimogene laherparepvec will be 21 days. On cycle 1, day 1, the first dose of talimogene laherparepvec will be up to 4.0 mL of 10^6 PFU/mL. During the second cycle, talimogene laherparepvec will be

administered up to 4.0 mL of 10^8 PFU/mL at week 4 of the study (**±** 3 days). During subsequent cycles, talimogene laherparepvec will be administered up to 4.0 mL of 10^8 PFU/mL every 21 days (± 3 days) thereafter. The maximum volume of talimogene laherparepvec to be administered at any dose is 4.0 mL for any individual tumor lesion or for all tumor lesions combined. Talimogene laherparepvec will be administered by image guided injection (either ultrasound or computerized tomography [CT]) into injectable liver lesions. After 6 cycles of intrahepatic talimogene laherparepvec are administered, there is an investigator option to continue talimogene laherparepvec injections for up to an additional 6 cycles (for a maximum of 12 total cycles of talimogene laherparepvec). During this additional dosing period (cycles 7 to 12), talimogene laherparepvec may be administered by intralesional injection to liver metastases or cutaneous, subcutaneous, and nodal tumor lesions, or both. For cycles 7 to 12, liver lesions do not need to be prioritized. Refer to Section 6.2.1.

Non-Amgen Investigational Product Dosage and Administration: Atezolizumab will be manufactured by Genentech. Atezolizumab is supplied as a single-use, 20-cc Pharmacopeia (USP)/European Pharmacopoeia (Ph. Eur.) type 1 glass vial as a colorless-to-slightly-yellow, sterile, preservative-free clear liquid solution intended for intravenous administration. The vial is designed to deliver 20 mL (1200 mg) of atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 20 mL volume. The first cycle of atezolizumab will be 21 (+ 3) days. Subsequent cycles of atezolizumab will be 21 (± 3) days. Atezolizumab will be administered intravenously at a dose of 1200 mg. Administration of atezolizumab will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies. The initial dose of atezolizumab (day 1, cycle 1) will be delivered over 60 (± 15) minutes. If the first infusion is tolerated without infusion-associated adverse events, the second infusion may be delivered over 30 (± 10) minutes. If the 30-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (± 10) minutes. The subject's vital signs should be determined up to 60 minutes before each atezolizumab infusion. Vital signs should also be obtained during or after the atezolizumab infusion if clinically indicated. Refer to Section 6.2.2.

Procedures: Written informed consent must be obtained from all subjects or legally acceptable representatives before any study specific screening procedures are performed. The following procedures will occur per the Schedule of Assessments: medical history, concomitant therapies, physical examination and vital signs, body weight, ECOG performance status, 12-lead electrocardiogram (ECG), recording of concomitant medications, survival assessment, review of adverse events, disease related events (serious or non-serious) and serious adverse events as well as reporting of potential or known unintended exposure to talimogene laherparepvec by a household member, caregiver, or healthcare provider. Blood will be collected for local laboratory testing including: urinalysis, chemistry, hematology, coagulation, thyroid function, hepatitis B surface antigen, hepatitis B core antibody, hepatitis C virus antibody and human immunodeficiency virus (HIV). Tumor markers in the blood will be collected in subjects with triple negative breast cancer (cancer antigen 27.29 [CA 27.29], cancer antigen 15-3 [CA 15-3]) and subjects with colorectal cancer (carcinoembryonic antigen [CEA] and CA-19-9). In females of childbearing potential serum pregnancy tests will be performed locally. Central laboratory testing will include blood for herpes simplex virus type 1 (HSV-1) serostatus, and blood for biomarker analysis. Liver tumor biopsies and clinical and radiological tumor assessments will also be performed.

For a full list of study procedures, including the timing of each procedure, please refer to Section 7 and the Schedule of Assessments (Table 7-1).

Statistical Considerations:

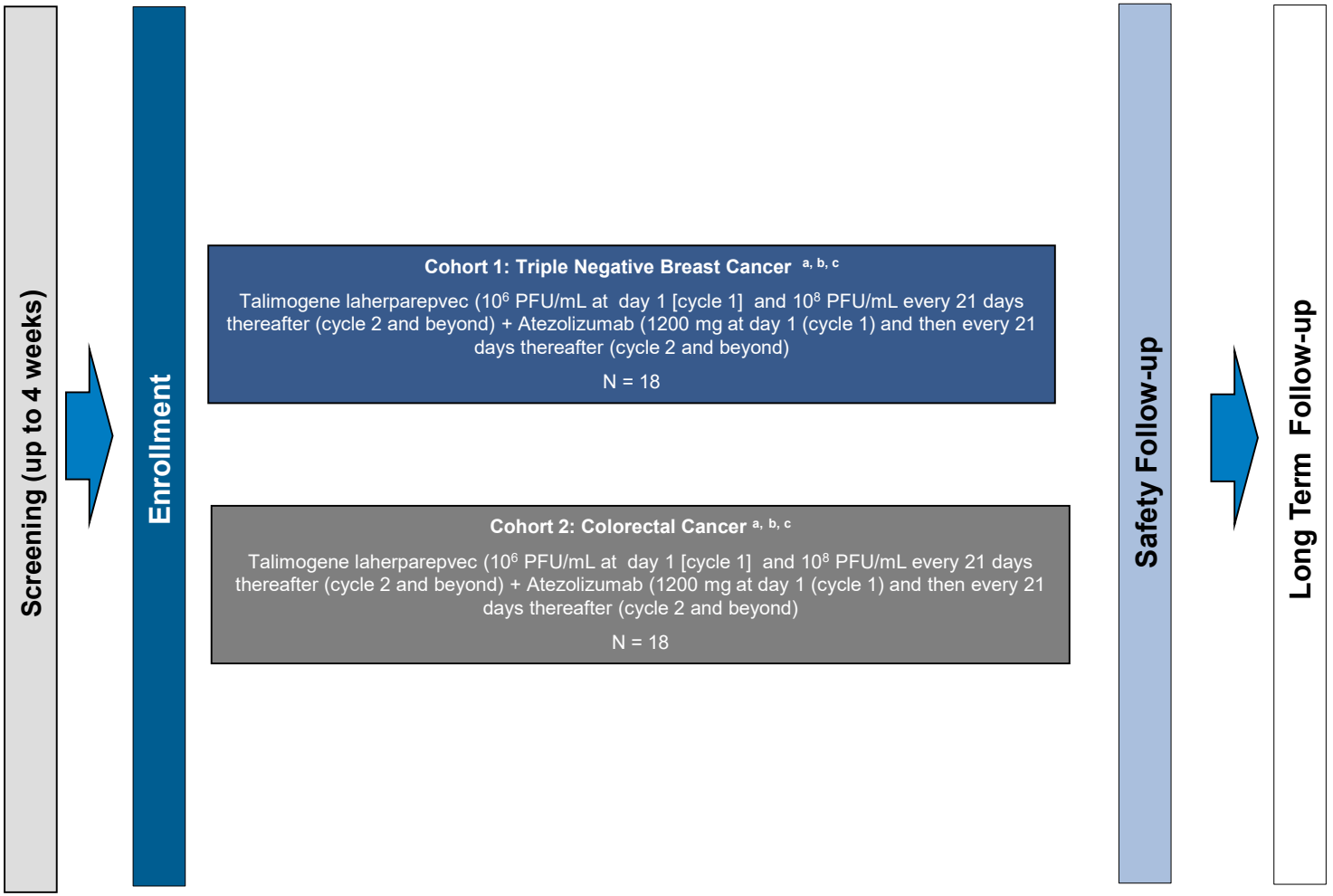
The null hypothesis (H0) is that the combination of talimogene laherparepvec and atezolizumab has a DLT rate ≤ 10%. An unacceptable alternative hypothesis (Ha) is a true DLT rate ≥ 33%. The sample size goal is to have ≥ 80% power for a 1-sided ≤ 10% significance level test to reject H0 when Ha is true (Goldman, 1987). Eighteen DLT-evaluable subjects in each cohort will be required to test H0. Assuming the incidence of DLTs is evaluated as specified by Table 3-1 in Section 3.1, this design achieves a 7.7% 1-sided significance level and 81.6% power. The data

will be analyzed by cohort. In addition, a summary of the incidence of DLTs and descriptive statistics for demographic, safety, efficacy, and biomarkers will be provided as appropriate. The DLT analysis set will be used to summarize the subject incidence of DLTs as defined in Section 6.2.1.2. The safety analysis set will be used for all safety analyses. The safety analyses include 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 efficacy analysis will be conducted using the safety analysis set unless otherwise specified. ORR, BOR, DRR, and DCR will be summarized with the associated 95% confidence interval (CIs). DOR, PFS, and OS will be summarized and estimated using the Kaplan-Meier method. Interim safety analyses will be performed for evaluation of DLTs for DLRT meetings. All available safety data will be considered at interim safety analysis. For a full description of statistical analysis methods, please refer to Section 10.

Sponsor: Amgen Inc.

Data Element Standards Version(s)/Date(s):	5/20 March 2015

Study Design and Treatment Schema



Footnotes defined on next page

PFU= plaque-forming unit

[a] Enrollment of cohort 1 and 2 will begin simultaneously. 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 atezolizumab and 3 weeks following the initial 10^8 PFU/mL dose of talimogene laherparepvec and atezolizumab or the start of cycle 3, whichever occurs first. DLTs will be evaluated based on the first 18 DLT-evaluable subjects in each cohort separately. A Dose Level Review Team (DLRT) will review the safety data to evaluate possible drug effects and DLT. To be evaluable for a DLT, subjects must have had the opportunity to be on treatment for at least 2 cycles from the initial dose of study treatments and have received at least 2 doses of talimogene laherparepvec and two doses of atezolizumab in combination, or have a DLT during the DLT evaluation period. For additional details see Section 3.1.

[b] Injection of non-hepatic lesions (nodal, cutaneous, or subcutaneous metastases) is permitted after the first tumor assessment (3 cycles) if volume remains after injecting liver lesions. After the initial 6 intra-hepatic cycles, there is an option to continue treatment with talimogene laherparepvec for an additional 6 cycles. During this additional dosing period (cycles 7 to 12), talimogene laherparepvec may be administered, by intralesional injection to liver metastases or cutaneous, subcutaneous, and nodal tumor lesions, or both. For cycles 7 to 12, liver lesions do not need to be prioritized. A maximum of 12 cycles of talimogene laherparepvec are allowed during the study. In the absence of confirmed PD per **modified** irRC-RECIST, atezolizumab treatment can continue after talimogene laherparepvec treatment has ended provided patient is tolerating atezolizumab and receiving clinical benefit in the opinion of the investigator.

[c] Treatment will continue until a subject experiences a DLT (during the DLT evaluation period), has CR, has need for an alternative anticancer therapy or experiences an adverse event necessitating drug discontinuation. In addition, treatment will be discontinued for talimogene laherparepvec if the subject has no injectable tumor lesions or upon confirmed PD per modified irRC-RECIST or rapid clinical deterioration. Atezolizumab will be discontinued upon symptomatic disease progression.

Study Glossary

Abbreviation or Term	Definition/Explanation
ALT	alanine aminotransferase
ALP	alkaline phosphatase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATA	anti-atezolizumab antibodies
BOR	best overall response
CA 19-9	cancer antigen 19-9
CA 27.29	cancer antigen 27.29
CEA	carcinoembryonic antigen
CI	confidence interval
CNS	central nervous system
CR	complete response
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	target trough concentration
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DCR	disease control rate
DILI	drug-induced liver injury
DLRT	Dose Level Review Team
DLT	dose limiting toxicity
dMMR	mismatch repair deficient
DNA	deoxyribonucleic acid
DOR	duration of response
DRR	durable response rate
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
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 endpoint(s), for the purpose of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early.

Abbreviation or Term	Definition/Explanation
End of Study (end of trial)	defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow up), as applicable. This will occur when the last subject discontinues talimogene laherparepvec or atezolizumab, whichever comes later, and has had the opportunity to complete both the safety follow-up 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
FDA	Food and Drug Administration
FOLFIRI	folinic acid-fluorouracil-irinotecan
GCP	Good Clinical Practice
GI	gastrointestinal
GM-CSF	granulocyte macrophage colony-stimulating factor
Heart rate	number of cardiac cycles per unit of time
HCC	hepatocellular carcinoma
HIV	human immunodeficiency virus
HR	hazard ratio
HSV, HSV-1	herpes simplex virus, herpes simplex virus type-1
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICP	infected cell protein
Ig	immunoglobulin
IT	intratumorally
IV	**intravenous**
INR	international normalization ratio
IPIM	Investigational Product Instruction Manual
IRB/IEC	institutional review board/independent ethics committee
irRC-RECIST	Immune Related Response Criteria simulating Response Evaluation Criteria in Solid Tumors
IxRS	interactive voice/web response system. A telecommunication technology that is linked to a central computer in real time as an interface to collect and process information.
LDH	lactate dehydrogenase
LAG-3	lymphocyte activation gene-3
MedDRA	Medical Dictionary for Regulatory Activities
MMR	mismatch repair
MSI-H	microsatellite instability-high
MSS	microsatellite stable

Abbreviation or Term	Definition/Explanation
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death 1
PD-L1	programmed death ligand 1
PET	positron emission tomography
PFS	progression-free survival
PFU	plaque-forming unit
Ph. Eur.	European Pharmacopoeia
PK	pharmacokinetics
POR	Proof of Receipts
PR	partial response
PR Interval	PR interval is measured from the beginning of the P wave to the beginning of the QRS complex in the heart's electrical cycle as measured by ECG
PT	prothrombin time
aPTT	activated partial thromboplastin time
PTT	partial thromboplastin time
qPCR	real-time polymerase chain reaction
QRS interval	QRS interval the interval between the Q wave and the S wave in the heart's electrical cycle as measured by ECG; represents the time it takes for the depolarization of the ventricles
QT interval	QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle as measured by ECG.
QTc interval	QT interval corrected for heart rate using accepted methodology
RANKL	nuclear factor-kappa B ligand
RECIST	Response Evaluation Criteria in Solid Tumors
SD	stable disease
SEERS	Surveillance, Epidemiology, and End Results
Source Data	information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline [E6]). Examples of source data include subject identification, randomization identification, and stratification value.

Abbreviation or Term	Definition/Explanation
Study day 1	defined as the first day that protocol-specified investigational products are administered to the subject
T3	triiodothyronine
T4	thyroxine
tk	thymidine kinase
TSH	thyroid stimulating hormone
TNF	tumor necrosis factor
TNF-α	tumor necrosis factor α
ULN	upper limit of normal
US	**United States**
USP	United States Pharmacopeia
WBC	white blood cells

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1. OBJECTIVES

1.1 Primary

To evaluate the safety, as assessed by incidence of dose limiting toxicities (DLTs), of intrahepatic injection of talimogene laherparepvec into liver metastases in combination with intravenously administered atezolizumab separately in subjects with triple negative breast cancer and colorectal cancer

1.2 Secondary

To evaluate the efficacy of talimogene laherparepvec in combination with atezolizumab separately in subjects with metastatic triple negative breast cancer and metastatic colorectal cancer with liver metastases assessed by:

- objective response rate (ORR), best overall response (BOR) , duration of response (DOR), lesion level responses in injected and uninjected lesions (overall, hepatic, nonhepatic) disease control rate (DCR) , durable response rate (DRR), progression-free survival (PFS), overall survival (OS) by cohort (triple negative breast cancer and colorectal cancer)

1.3 Safety

To evaluate the safety and tolerability of intrahepatic injection of talimogene laherparepvec into liver metastases in combination with intravenously administered atezolizumab separately in subjects with triple negative breast cancer and colorectal cancer

1.4 Exploratory

The exploratory objectives of the study are as follows:

- To evaluate changes in tumor inflammation markers in tumor biopsies, such as programmed cell death ligand 1 (PD-L1) expression and cluster of differentiation 8 (CD8) density
- To explore blood and tissue biomarkers that may correlate with or predict treatment effect and/or clinical outcomes separately in subjects in triple negative breast cancer and metastatic colorectal cancer.

2. BACKGROUND AND RATIONALE

2.1 Disease

2.1.1 Cancer and Immunotherapy

Clinical study data have shown that immune therapies are valid approaches in cancer therapy. Immune checkpoint blocking monoclonal antibodies can provide durable responses and improve OS in cancer patients (Hodi et al, 2010; Garon et al, 2014).

Tumor-specific mutations may be an important stimulus of responsiveness to immune-based therapies and are currently being evaluated in different tumor types.

Human cancer cells are characterized by a multitude of genetic aberrations (Alexandrov et al, 2013; Lawrence et al, 2013), many of which may be associated with immunogenicity by presenting novel epitopes for immune-cell recognition (Segal et al, 2008). The immune response, largely mediated by tumor-reactive T cells, can be rapid, durable, and adaptable. A recent study demonstrated that novel epitopes generated from missense mutations may be the target of tumor-reactive T cells and may mediate response to T cell checkpoint inhibitors (van Rooij et al, 2013). Moreover, the durable responses observed in a subset of patients long after completion of therapy suggest the generation of T cell memory, which has been associated with improved overall survival in cancer patients (Pages et al, 2005; Kilinc et al, 2009).

The immune system recognizes and is poised to eliminate cancer but is held in check by inhibitory receptors and their ligands. These immune checkpoint pathways, which normally maintain self-tolerance and limit collateral tissue damage during anti-microbial immune responses, can be co-opted by cancer cells to evade immune destruction (Topalian et al, 2012). Monoclonal antibodies have been developed that will block specific immune checkpoint proteins and unleash anti-tumor activity. Available approved immune checkpoint inhibitors include ipilimumab, nivolumab, pembrolizumab, and atezolizumab. Ipilimumab blocks cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) thereby prolonging T cell activation, restoring T cell proliferation, and amplifying T cell-mediated immunity. Nivolumab and pembrolizumab are antibodies that will block programmed cell death 1 (PD-1) on the surface of the T cells preventing them from interacting with PD-L1. Atezolizumab blocks PD-L1. Immune-based therapies are only effective in a proportion of patients with cancer, and combination approaches are being explored to improve therapeutic efficacy.

PD-1 is an inhibitory receptor expressed on T cells following T cell activation, which is sustained in states of chronic stimulation such as in chronic infection or cancer (Blank et al, 2005; Keir et al, 2008). Ligation of PD-L1 with PD-1 inhibits T cell proliferation, cytokine production, and cytolytic activity, leading to the functional inactivation of T cell responses. Aberrant expression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen, 2007). Therefore, interruption of the PD-L1/PD-1 pathway represents an attractive strategy to reinvigorate tumor-specific T cell immunity.

PD-L1 expression is prevalent in many human tumors, and elevated PD-L1 expression is associated with a poor prognosis in patients with non–small cell lung cancer

(Mu et al, 2011) and other solid tumors (Hino et al, 2010; Hamanishi et al, 2007; Thompson et al, 2006).

The field of cancer immunotherapy is expanding beyond checkpoint inhibition to include such categories as T cell growth factors/stimulators, cancer vaccines, inhibitors of cancer cell and immune cell suppression, dendritic cell growth factors and activators. Oncolytic immunotherapy is an emerging treatment modality which uses replication competent oncolytic viruses that will selectively infect and damage cancerous tissues without causing harm to normal tissues. Each oncolytic virus has a specific cellular tropism that determines which tissues are preferentially infected and genetic engineering can be used to make them cancer specific while rendering them nonpathogenic to normal host cells (Russell et al, 2014). Ongoing studies are using a variety of engineered viruses, including but not limited to herpes simplex virus (HSV), vaccinia, and reovirus.

2.1.2 Metastatic Triple Negative Breast Cancer

The incidence rate of breast cancer varies worldwide and the mortality rate is between 10 and 20 per 100,000 women across most global regions (Youlden et al, 2012). Annually in the United States, approximately 232,000 women are diagnosed with and 40,290 women die from breast cancer according to the Surveillance, Epidemiology, and End Results (SEER) Program. Triple negative tumors account for about 15% of all invasive breast cancers (Foulkes et al, 2010). Among metastatic triple negative cases, the first distant site is lung (40%), brain (30%), liver (20%), and bone (10%) (Foulkes et al, 2010). With subsequent metastases, the liver will be diagnosed as a metastatic site in up to 50% of women with metastatic triple negative breast cancer (Lin et al, 2008). The estimated 5-year survival rate for metastatic triple negative breast cancer is approximately 22% according to the SEER database. Incidence of triple negative breast cancer is increased in patients with germline breast cancer susceptibility gene 1 (BRCA1) mutations and African ancestry. Triple negative breast cancers are generally, aggressive tumors with a high rate of distant metastases and worse disease-specific survival than other breast cancer subtypes (Dent et al, 2007; Haffty et al, 2006). Tumors with the triple negative phenotype have specific features that are potential therapeutic targets (eg, they show an impaired deoxyribonucleic acid (DNA) repair mechanism and increased expression of basal-associated and proliferation associated markers). Currently, the main treatment modality used is chemotherapy but

other targets are currently being investigated including the DNA repair pathway, angiogenesis and epidermal growth factor receptor (Rakha et al, 2011).

There is significant heterogeneity within triple negative breast cancer. A study analyzing gene expression profiling identified 6 subtypes, one of which was an immunomodulatory subtype enriched for genes involved in immune cell processes including immune cell signaling, cytokine signaling, antigen processing and presentation, and signaling through core immune signal transduction pathways (Lehmann et al, 2011). In addition, the clinical importance of tumor immune infiltrates has been an emerging area of research in triple negative breast cancer, where an increased number of immune infiltrates seems to predict both response to chemotherapy and improved survival in the neoadjuvant setting and is a prognostic factor in the adjuvant setting (Adams et al, 2014; Dieci et al, 2014, Ono et al, 2012).

2.1.2.1 Immunotherapy in Triple Negative Breast Cancer

Clinical studies in breast cancer to date have focused on countering immune suppression by targeting the lymphocyte activation gene-3 (LAG-3), CTLA-4 or PD-L1 pathways. PD-L1 is expressed in approximately 20% of patients with triple negative breast cancer and treatment with anti PD-1 and anti PD-L1 agents (eg, pembrolizumab, atezolizumab, nivolumab) is currently under investigation in several ongoing trials.

Data indicate that PD-1/PD-L1 pathway blockade has clinical activity in patients with metastatic triple negative breast cancer. Atezolizumab (anti-PD-L1) is being evaluated in an ongoing phase 1a study exploring its safety and efficacy, as well as biomarkers of response in a variety of cancers. One expansion cohort has enrolled patients with both PD-L1 positive and PD-L1 negative triple negative breast carcinoma (Emens et al, 2015). Tumors were considered to be PD-L1 positive if ≥ 5% of infiltrating immune cells stained for PD-L1 expression by immunohistochemistry. Among prescreened patients, 23% were PD-L1 positive at first report. Enrolled patients were heavily treated, with 89% having received more than 4 lines of systemic therapy. Atezolizumab was given at 15 or 20 mg/kg of a 1,200 mg flat intravenous dose every 3 weeks. Atezolizumab was well tolerated in 54 patients with PD-L1 positive and PD-L1 negative disease who were evaluable for safety. Low-grade adverse events, including fatigue, nausea, fever, anorexia, and asthenia, were observed in 63% of patients, while 11% of patients experienced grade 3 treatment-related adverse events. There was 1 case of grade 4 pneumonitis, and 2 deaths currently assessed as related by the investigator are under active investigation. The ORR for 21 PD-L1 positive

patients with metastatic triple negative breast cancer evaluable for efficacy was 19%, including 2 CRs and 2 PRs; 3 of 4 of these responses were ongoing at the time of data cutoff. Three additional patients had clinical benefit in the setting of a nonclassical response, with durable regression of target lesions, even though new lesions developed. Pharmacodynamic changes associated with PD-L1 inhibition included transient increases in the number of activated, proliferating CD8+ T cells and increased levels of interleukin-18. After initial evidence of activity in triple negative breast cancer subjects in a phase 1/2 study, atezolizumab **was** evaluated in combination with nab-paclitaxel in a **randomized** phase 3 trial (NCT02425891) **of 902 patients with untreated metastatic triple negative breast cancer who were randomized 1:1 to atezolizumab plus nab-paclitaxel or placebo plus nab-paclitaxel. Median OS in the atezolizumab plus nab-paclitaxel arm was 21.3 months, and in the placebo plus nab-paclitaxel arm was 17.6 months (Hazard ratio for death, 0.84; P = 0.08); in patients with PD-L1 positive tumors, the median OS was 25.0 months for the atezolizumab plus nab-paclitaxel arm and 15.5 months for the placebo plus nab-paclitaxel arm (Hazard ratio 0.62). The rate of grade 3 or 4 adverse events was 48.7% in the atezolizumab plus nab-paclitaxel group and 42.2% in the placebo plus nab-paclitaxel group, with the most common being neutropenia, decreased neutrophil count, peripheral neuropathy, fatigue, and anemia. 57.3% in the atezolizumab plus nab-paclitaxel group and 41.8% in the placebo plus nab-paclitaxel group had an adverse event of special interest, suggestive of a potential immune-related etiology. Grade 3 or 4 adverse events of special interest occurred in 7.5% in the atezolizumab plus nab-paclitaxel group and 4.3% in the placebo plus nab-paclitaxel group. One grade 5 event of special interest (autoimmune hepatitis) occurred in the atezolizumab plus nab-paclitaxel group, and one grade 5 event of special interest (hepatic failure) occurred in the placebo plus nab-paclitaxel group. Adverse events that led to discontinuation of any agent occurred in 15.9% of subjects who received atezolizumab plus nab-paclitaxel, and in 8.2% of subjects who received placebo plus nab-paclitaxel. 6.4% discontinued atezolizumab because of adverse events, and 1.4% discontinued placebo because of adverse events. Based on the results of this trial, on March 8, 2019, the United States (US) Food and Drug Administration (FDA) granted accelerated approval for atezolizumab in combination with nab-paclitaxel for initial treatment of adult patients with unresectable locally advanced or metastatic triple negative breast cancer whose tumors express PD-L1, as determined by an FDA-approved test.**

Pembrolizumab was evaluated in 32 patients with advanced PD-L1 positive triple negative breast carcinoma. (Nanda et al, 2014). Of all patients screened, 58% had PD-L1 staining in the tumor stroma or in ≥ 1% of tumor cells. Most patients treated with pembrolizumab had received 1 to 3 prior chemotherapy regimens for metastatic disease, and 21.9% had received 5 or more. Patients received pembrolizumab at a dose of 10 mg/kg intravenously (IV) every 2 weeks. Adverse events were generally manageable, with 5 grade 3/4 toxicities. There was also 1 treatment-related death due to disseminated intravascular coagulation. The ORR for 27 evaluable patients was 18.5%, including 1 CR and 2 partial response (PR). The median time to response was 18 weeks (range, 7 to 32 weeks), with the median DOR not reached. The 6-month PFS rate was 23.3%.

Preclinical data with engineered oncolytic viruses have shown efficacy in breast cancer tumor models (Cody et al, 2015). Fourteen patients with breast cancer were treated in the first-in-human study with talimogene laherparepvec (Hu et al, 2006). Overall safety and evidence of efficacy (evidenced by tumor necrosis with HSV antigen detection in necrotic areas) in biopsy specimens was demonstrated. Some breast cancer patients showed stable disease (SD) in the injected lesions and/or shrinkage of both injected and adjacent uninjected tumor lesions. Additionally, the oncolytic herpes simplex virus type 1 (HSV-1) mutant (HF10) has been used in a pilot study involving direct intratumoral injection in 6 patients with recurrent breast cancer and was shown to be well tolerated (Kimata et al, 2006). A follow-up study showed histological evidence of viral replication and CD8+ lymphocyte infiltration in injected tumors (Sahin et al, 2012). A phase 2 study of reolysin for patients with advanced/metastatic breast cancer is ongoing (NCT01656538).

2.1.3 Metastatic Colorectal Cancer

Colorectal cancer incidence rates vary worldwide, with rates per 100,000 among males ranging from 4 in India to 59 in the Czech Republic (Center et al, 2009). Annually in the United States, approximately 132,700 people are diagnosed with and 49,700 people die from colorectal cancer (SEER). The proportion of patients with synchronous liver metastases at initial diagnosis is about 15% and the 5-year cumulative metachronous liver metastasis rate has been reported to be 4% for stage I tumors, 13% for stage II, and 30% for stage III (Manfredi et al, 2006). For 3 of 4 cases at diagnosis of liver metastasis, the liver is the only metastatic site (Manfredi et al, 2006).

Microsatellite instability-high (MSI-H) colorectal cancer comprises approximately 15% of sporadic colorectal cancer and most familial colorectal cancer, whereas the remainder are microsatellite stable (MSS) (Smyrk et al, 2001). Cells with abnormal mismatch repair function accumulate DNA replication errors. The high mutational load in MSI-H tumors also creates many tumor-specific neoantigens, typically 10 to 50 times those of MSS tumors (Llosa et al, 2015). Llosa and colleagues analyzed surgically resected primary sporadic colorectal cancer tissue and found that a subset displayed high infiltration of activated CD8+ cytotoxic T lymphocytes as well as activation of additional cytokines where nearly all of the tumors of this subset demonstrated microsatellite instability. Compared with MSS tumors, MSI-H tumors highly upregulate expression of multiple immune checkpoints, including PD-1 and CTLA-4, PD-L1, LAG-3, and indolamine 2, 3-dioxygenase in either tumor infiltrating lymphocytes, stroma or both. Because most MSI-H colorectal cancers typically present with lower-stage disease than MSS colorectal cancers, the MSI-H subtypes represent only 5% to 6% of the stage IV colorectal cancer population (Lochhead et al, 2013).

2.1.3.1 Immunotherapy in Colorectal Cancer

Clinically, there is evidence of activity of PD-1 based therapy in colorectal cancer. In a phase 1 study of nivolumab that included 39 patients with various solid tumors, 1/14 patients with metastatic MSI-H colorectal cancer had a durable CR (Brahmer et al, 2012). Interestingly, a pretreatment tumor specimen revealed membranous expression of PD-L1 on tumor-infiltrating macrophages and lymphocytes and on rare tumor cells, as well as PD-1-positive CD3+ T cells (Lipson et al, 2013). Additionally, a phase 2 investigator-initiated study with 41 patients demonstrated that the mismatch repair deficient (dMMR) phenotype is predictive of responses to PD-1 blockade. Administration of pembrolizumab monotherapy resulted in objective response of 40% of patients with dMMR colorectal tumors compared with 0% in patients with MMR proficient colorectal cancer. Median PFS and OS were not reached in the dMMR colorectal cancer cohort versus 2.2 and 5.0 months in the MMR proficient cohort, and somatic mutational burden correlated with PFS (Le et al, 2015). Based on this and other data, the U.S. FDA has granted Breakthrough Therapy Designation to pembrolizumab for the treatment of patients with MSI-H metastatic colorectal cancer, and on 23 May 2017, granted accelerated approval to pembrolizumab for adult and pediatric patients with unresectable or metastatic, MSI-H or dMMR solid tumors that have progressed on prior therapy.

Although the exact mechanism of checkpoint inhibitors in colorectal cancer is still unknown, these agents function by releasing inhibition of the immune response, and therefore they likely act in large part by enhancing pre-existing antigenic responses. Preclinical data has suggested that administration of replication competent HSV-1 oncolytic virus to nude rat tumors was successful in suppressing tumor growth and killing human colorectal cancer cells efficiently (Kooby et al, 1999). A phase 1 study of intravenous reolysin (non-enveloped human reovius) in combination with folinic acid-fluorouracil-irinotecan (FOLFIRI) and bevacizumab in FOLFIRI-naive patients with KRAS mutant metastatic colorectal cancer is currently ongoing. The primary endpoint is safety, and the secondary endpoint examines biomarkers and efficacy parameters (NCT01274624).

2.1.4 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 hepatocellular carcinoma (HCC) or metastatic liver tumors (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 tumor swelling and obstruction of the intrahepatic bile duct and grade 3 anorexia and abdominal pain. 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 a PR (lung squamous cell carcinoma, HCC, and melanoma), and 6 had SD by Response Evaluation Criteria in Solid Tumors (RECIST). By Choi response criteria (a criteria initially developed for gastrointestinal (GI) stromal tumors which assesses change in size and change in density of target lesions), an additional 5 subjects with SD by RECIST were found to also have a PR (colorectal cancer, 2 subjects and renal cell carcinoma, thymic squamous cell carcinoma, and extragonadal germ cell tumor). 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 1 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 (intravenous), 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 (NCT02562755).

NV1020, an attenuated derivative of HSV-1 that has deletions of the genes encoding infected cell protein (ICP) 34.5, UL56, UL24, and tk and reinsertion of a functional HSV-1 tk gene, was administered into the liver intra-arterially for unresectable colorectal cancer liver metastases in a phase 1/2 study (Geevarghese et al, 2010). Doses from 3 x 10^6 to 1 x 10^8 PFU were administered for up to 4 infusions to 13 subjects in the dose-escalation phase 1 portion, and no DLTs were seen. For phase 2, the 1 x 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 x 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.

2.2 Amgen Investigational Product Background: Talimogene Laherparepvec

Talimogene laherparepvec is a virally-based oncolytic immunotherapy consisting of an immune-enhanced HSV-1 that selectively replicates in solid tumors. In this genetically modified strain, the HSV-1 viral genes encoding ICP 34.5 (a neurovirulence factor) and ICP47 (which blocks viral antigen presentation to major histocompatibility complex class I) have been functionally deleted. The coding sequence for GM-CSF has been inserted in place of ICP34.5 and is intended to enhance the immune response to tumor antigens released after virus replication and lytic tumor cell death. Thus, talimogene laherparepvec has 2 mechanisms of action: (a) direct oncolysis of infected tumor cells

and (b) immune activation through tumor-associated antigen release, innate immune activation and local virus-mediated GM-CSF expression. Talimogene laherparepvec is administered by direct injection into tumors.

In the United States, talimogene laherparepvec (Imlygic®) is indicated for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery. The indication also contains a limitation of use which states that talimogene laherparepvec has not been shown to improve overall survival or have an effect on visceral metastases. Additionally, in the European Union, talimogene laherparepvec (Imlygic®) has been approved for the treatment of adults with unresectable melanoma that is regionally or distantly metastatic (Stage IIIB, IIIC, and IVM1a) with no bone, brain, lung or other visceral disease.

As of 26 April 2016, more than 1,000 patients have received talimogene laherparepvec with approximately 761 patients having received talimogene laherparepvec in research studies and approximately 350 people were prescribed talimogene laherparepvec (IMLYGIC®) after it was approved for sale in the United States.

In the First-in-Human Study, 001/01, talimogene laherparepvec was administered in single ascending doses of 10^6, 10^7, or 10^8 plaque forming unit (PFU)/mL (up to 4 mL) to subjects with breast cancer, colorectal cancer, head and neck cancer, and melanoma with refractory cutaneous or subcutaneous metastases (Hu et al, 2006). In the first 2 single-dose cohorts, subjects who were HSV-1 seronegative at study entry experienced more adverse events, including febrile influenza-like syndromes associated with symptoms of fatigue, rigors, erythematous skin rashes and small vesicles in the skin. At the highest dose (10^8 PFU/mL), only HSV-1 seropositive subjects received talimogene laherparepvec and no rashes or rigors were observed. In the subsequent multidose part of the study, talimogene laherparepvec was well tolerated in HSV-1 seronegative as well as seropositive subjects who received a first dose of 10^6 PFU/mL, followed by 2 doses of 10^8PFU/mL. Febrile responses were minimal. Of the 17 subjects, 7 subjects were HSV-1 seronegative at baseline but within 21 days (3 weeks) after the initial dose of 10^6 PFU/mL was administered, 6 of the 7 subjects seroconverted. Based on these findings, to facilitate tolerance, enable seroconversion, and ensure consistency in dosing, the recommended dose in adults (both HSV-1 seropositive and seronegative groups) was established to be 10^6 PFU/mL followed by 10^8 PFU/mL 21 days (3 weeks) later. Subsequent dosing could safely be administered every 14 days (2 weeks).

In the melanoma setting, talimogene laherparepvec has been administered into cutaneous or subcutaneous lesions or lymph nodes accessible by ultrasound. The largest study to evaluate the activity of talimogene laherparepvec in melanoma was the pivotal OPTiM study. 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, and 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, 2015b).

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 ≥ 50% and 100%, respectively, demonstrating the systemic effect of talimogene laherparepvec beyond injected lesions (Andtbacka et al, 2014, Andtbacka et al, 2015a).

The most common side effects in the OPTiM study were chills (talimogene laherparepvec, 49%; GM-CSF, 9%), pyrexia (43%; 9%), injection-site pain (28%; 6%), nausea (36%; 20%), influenza-like illness (30%; 15%), and fatigue (50%; 36%). Grade ≥ 3 adverse events occurred in 36% of subjects receiving talimogene laherparepvec and 21% of subjects receiving GM-CSF. The only grade 3/4 adverse events occurring in ≥ 5 subjects was cellulitis (talimogene laherparepvec, n=6 [2.1%]; GM-CSF, n=1 [<1%]). Of 10 fatal adverse events in the talimogene laherparepvec arm, eight were attributable to disease progression. The remaining two fatal adverse events (sepsis in the setting of salmonella infection; myocardial infarction) were not considered treatment-related per investigator (Andtbacka et al, 2015a).

The injection of talimogene laherparepvec into visceral tumors has been studied in the 005/04 phase 1 study for advanced pancreatic cancer in subjects who either failed standard therapy or could not receive/refused standard 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 (cohort 1, n=3), 1 dose of 10^5 PFU/mL followed by 2 doses of 10^6 PFU/mL every 3 weeks (cohort 2, n=4), or 1 dose of 10^6 PFU/mL followed by 2 doses of 10^7 PFU/mL every 3 weeks (cohort 3, n=10). A fourth dose schedule of 10^6 PFU/mL followed by 2 doses of 10^8 PFU/mL every 3 weeks was planned but not opened because the study was terminated early. 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 post-dose 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 (2 in cohorts 1 and 1 in cohort 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.

There are currently 4 ongoing combination immunotherapy studies with talimogene laherparepvec and a checkpoint inhibitor in advanced stage melanoma. One is a phase 1b/2 study of ipilimumab with or without talimogene laherparepvec in unresected melanoma (NCT01740297). In the phase 1b portion, 18 of 19 subjects (more than half with visceral disease) received both talimogene laherparepvec and ipilimumab in combination. Full dose of talimogene laherparepvec and ipilimumab 3 mg/kg every 3 weeks starting week 6 were tolerable. Per immune-related response criteria (data cutoff of 22 December 2014), the ORR in 18 evaluable subjects was 56% (33% CRs), and the DRR was 44%. Median PFS was 10.6 months (2.6 to 19.3+ months). Median OS was not reached; 12-month and 18-months survival rates were 72.2% and 67%, respectively. On a lesion level, 8 and 5 of 16 uninjected index lesions regressed ≥ 50% and 100%, respectively. Grade 3/4 treatment-emergent adverse events occurred in 32% of subjects, and grade 3/4 immune-related adverse events occurred in two subjects (grade 3 hypophysitis and adrenal insufficiency; and grade 4 amylase + lipase elevations). There were no treatment-related deaths (Puzanov et al, 2014). Another study is a phase 1b/3 multicenter open-label trial of talimogene laherparepvec in combination with pembrolizumab for treatment of unresected, stage IIb to IVM1c melanoma (NCT02263508). In the phase 1b portion of the study, subjects with stage IIB-IV melanoma with injectable lesions and no prior systemic therapy received up to 4.0 mL of talimogene laherparepvec monotherapy for 2 doses followed by talimogene laherparepvec and pembrolizumab every 2 weeks thereafter. All 21 evaluable subjects had an adverse event: 29% grade 3, no grade 4 and one grade 5 (not treatment related). The most common adverse events by preferred term were fatigue (52%), pyrexia (48%), chills (43%), and rash (38%). Of 16 subjects evaluable for response, the unconfirmed response rate per investigator was 56%; DCR was 69% (12.5% CR, 44% PR, 12.5% SD) (Long et al, 2015).

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 (Amgen data on file). Additionally, a dose escalating hepatic injection study with talimogene laherparepvec into HCC and metastatic liver tumors is currently ongoing

(NCT02509507). In that study, talimogene laherparepvec was shown to be safe when administered intrahepatically into non-HCC liver metastases at up to 4 mL of 10^6 PFU/mL initial dose followed 3 weeks later by up to 4 mL of 10^8 PFU/mL every 3 weeks (Hecht et al, 2018).

The current study combining talimogene laherparepvec and atezolizumab will use the dose of talimogene laherparepvec that has been demonstrated to be safe in the monotherapy setting.

Refer to the specific section of the talimogene laherparepvec Investigator's Brochure for additional information related to the physical, chemical, and pharmaceutical properties and formulation(s).

2.3 Non-Amgen Investigational Product Background: Atezolizumab

Atezolizumab is a humanized immunoglobulin (Ig) G1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors , PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al, 2016; Rosenberg et al, 2016). Atezolizumab has minimal binding to Fc receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and cancer patients and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy.

Atezolizumab is approved in the United States and other countries for the treatment of urothelial carcinoma and is approved in the United States for the treatment of non–small cell lung cancer**. It is also approved in the United States in combination with nab-paclitaxel for the treatment of PD-L1 positive triple negative breast cancer** (refer to the prescribing information for specific indications).

Refer to the Atezolizumab Investigator's Brochure for details on nonclinical and clinical studies.

2.4 Rationale

Talimogene laherparepvec and atezolizumab blockade may 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. Data indicate that the PD-L1/PD-1 pathway plays a role in triple negative breast cancer. Its role in colorectal cancer is currently being explored. Atezolizumab is a PD-L1 regulator and prevents T cell exhaustion in peripheral tissues.

The combination of an agent that increases tumor-specific immune activation (talimogene laherparepvec) with one that blocks inhibitory T cell checkpoints (atezolizumab) could potentially produce greater antitumor activity than either agent alone in both triple negative breast cancer and colorectal cancer. The aim of this study is to evaluate safety and explore efficacy of the two agents in combination.

2.5 Clinical Hypotheses

It is hypothesized that intrahepatic injection of talimogene laherparepvec in combination with intravenously administered atezolizumab in subjects with triple negative breast cancer and colorectal cancer with liver metastases will be safe and well tolerated with a DLT rate ≤ 10%.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a phase 1b, multicenter, open-label study to evaluate the safety of intrahepatic injection of talimogene laherparepvec in combination with intravenously administered atezolizumab in subjects with triple negative breast cancer and colorectal cancer with liver metastases. Approximately 36 **DLT-evaluable** subjects will be enrolled in two parallel cohorts. Cohort 1 will comprise triple negative breast cancer subjects with liver metastases (n = 18 **DLT-evaluable subjects**). Cohort 2 will comprise subjects with colorectal cancer with unresectable liver metastases (n = 18 **DLT-evaluable subjects**). Subjects will be treated with up to 4.0 mL of 10^6 PFU/mL talimogene laherparepvec at cycle 1, day 1 followed by talimogene laherparepvec up to 4.0 mL of 10^8 PFU/mL 21 **±** 3 days later (cycle 2, day 1, week 4 of the study). Subsequent cycles of up to 4.0 mL of 10^8 PFU/mL talimogene laherparepvec will be given every 21 (± 3 days). The first cycle of atezolizumab will be 21 (+ 3) days. Subsequent cycles of atezolizumab will be 21 (± 3) days. Atezolizumab will be administered intravenously at a dose of 1200 mg. For further details see Section 6.2.1.1 and 6.2.2.1.

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 atezolizumab and 3 weeks following the initial 10^8 PFU/mL dose of talimogene laherparepvec and atezolizumab or the start of cycle 3, whichever occurs first. DLTs will be evaluated based on the first 18 DLT-evaluable subjects in each cohort separately according to Table 3-1. The definition of DLT is provided in Section 6.2.1.2.3.

A Dose Level Review Team (DLRT) will review the safety data to evaluate possible drug effects and DLT. To be evaluable for a DLT, subjects must have had the opportunity to be on treatment for at least 2 cycles from the initial dose of study treatments and have received at least 2 doses of talimogene laherparepvec and two doses of atezolizumab in combination, or have a DLT during the DLT evaluation period. Subjects may be replaced if they are not evaluable for DLT in order to obtain 18 DLT-evaluable subjects.

Safety will be evaluated considering the incidence of DLTs among all DLT-evaluable subjects enrolled in the study in each cohort. A sequential stopping rule is derived based on a hypothesis testing approach (Goldman, 1987). There will be one safety interim analysis after the first 4 to 6 DLT-evaluable subjects have been enrolled in this study and a safety analysis after 18 DLT-evaluable subjects have been enrolled in a cohort. Enrollment will be suspended during the first safety interim analysis. At the discretion of the DLRT, additional safety analyses may be conducted as warranted. The cumulative increments of DLT-evaluable subjects and corresponding acceptable maximum number and percentage of DLTs at each analysis are shown in Table 3-1. The combination will not be declared safe if the number of DLTs exceeds the acceptable maximum number and enrollment will stop.

Table 3-1. Cumulative Increments of DLT-evaluable Subjects and Corresponding Acceptable Maximum Number and Percentage of DLTs at Each Interim Safety Analysis

Number of subjects	Acceptable Maximum Number (%) of DLTs	Stopping Number (%) of DLTs
2	1 (50)	2 (100)
3	1 (33)	2 (66)
4	2 (50)	3 (75)
5	2 (40)	3 (60)
6	2 (33)	3 (50)
7	2 (29)	3 (43)
8	2 (25)	3 (38)
9	3 (33)	4 (44)
10	3 (30)	4 (40)
11	3 (27)	4 (36)
12	3 (25)	4 (33)
13	3 (23)	4 (31)
14	4 (29)	5 (36)
15	4 (27)	5 (33)
16	4 (25)	5 (31)
17	4 (24)	5 (29)
18[a]	4 (22)	5 (28)

DLT = dose limiting toxicity
The design achieves a 7.7% 1-sided significance level and 81.6% power to test the null hypothesis of a DLT rate ≤ 10% versus the alternative hypothesis of a rate ≥ 33%.
[a] If > 18 subjects receive the combination they will contribute to the overall safety analysis, but only the first 18 DLT-evaluable will be considered in the decision to declare the combination safe.

Treatment will continue until a subject experiences a DLT (during the DLT evaluation period). See Section 6.2.1.3 and Section 6.2.2.2 for other reasons for stopping treatment.

All subjects will complete a safety follow-up visit approximately 30 (+ 7) days after the last dose of study treatment. Adverse events and disease related events will be collected as described in Section 9.2. After the safety follow-up visit, all subjects will enter the long-term follow-up. Subjects will be followed for survival, subsequent anticancer therapies and treatment related adverse events every 12 weeks (± 28 days) for approximately 24 months after the last subject is enrolled.

Subjects who have received talimogene laherparepvec and completed the protocol-specified long-term follow-up period for a reason other than death or withdrawal of full consent will be eligible to continue follow-up in a separate ongoing registry study which is in place for the long-term survival follow-up of subjects treated with talimogene

laherparepvec in clinical trials. The registry study will also monitor for late and long-term adverse events thought to be potentially related to talimogene laherparepvec.

The overall study design is described by a study schema at the end of the protocol synopsis section.

The study endpoints are defined in Section 10.1.1.

3.2 Number of Sites

The study will be conducted at approximately 20 sites in the United States of America (USA), Europe, and Australia.

3.3 Number of Subjects

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

Approximately 36 **DLT-evaluable** subjects will be enrolled (18 **DLT-evaluable** subjects in each cohort). Refer to Section 10.2 for sample size considerations.

3.4 Replacement of Subjects

Subjects enrolled may be replaced if they are not evaluable for DLT (eg, a subject did not receive at least one dose of each investigational agent, or ended the study treatment before completion of DLT evaluation period for a reason other than experiencing a DLT).

3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

The duration of screening for each subject will be up to 28 days (4 weeks). The subject accrual period is planned to be approximately 12 months. The duration of treatment will vary for each subject. Subjects may receive a maximum of 12 cycles of talimogene laherparepvec. All subjects will complete a safety follow-up visit approximately 30 (+ 7) days after the last dose of study treatment. After the safety follow-up visit subjects will enter the long-term follow-up. During this period, subjects will be followed every 12 weeks (± 28 days) for survival for up to approximately 24 months after the last subject is enrolled. The study duration for an individual subject may be up to approximately 3 years.

3.5.2 End of Study

Primary Completion: The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), for the purpose of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early.

The primary completion date is the date when data for the primary endpoint are last collected for the purposes of conducting the primary analysis.

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

4. SUBJECT ELIGIBILITY

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

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

4.1 Inclusion Criteria

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

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

103 Histologically or cytologically confirmed diagnosis of triple negative breast cancer or colorectal cancer with liver metastases

104 Subjects with triple negative breast cancer with liver metastases, or subjects with colorectal cancer with liver metastases are eligible if they have had disease progression during or after ≥ 1 prior standard of care systemic anti-cancer therapy (eg, chemotherapy, targeted therapy) for metastatic disease **or if they progress during or within 6 months of receiving adjuvant therapy. If subjects, in the opinion of the investigator, are deemed not appropriate candidates for systemic anti-cancer therapy for metastatic disease or if they refuse systemic anti-cancer therapy for metastatic disease, they may be eligible after investigator discussion with sponsor medical monitor for approval.**

105 Measurable disease as defined by:

- ≥ 1 metastatic liver lesion that can be accurately and serially measured in ≥ 1 dimension and for which the longest diameter is ≥ 1 cm as measured by multiphase CT scan or magnetic resonance imaging (MRI)
- Measureable metastatic liver lesion(s) must not be in 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 can be measured and distinguished from the effects of any anti-cancer therapy prior to enrollment

106 Candidate for intrahepatic injection as defined by:

- ≥ 1 injectable metastatic liver lesion without necrosis ≥ 1 cm in longest diameter or ≥ 1 metastatic liver lesion with necrosis where the longest diameter of the necrotic region subtracted from longest diameter of the lesion is ≥ 1 cm
- metastatic liver lesions selected for injection must not be located where any potential tumor swelling after injection may lead to biliary tract obstruction (eg, < 1 cm adjacent to the left main, right main, or common biliary ducts) or where there may be risk of bleeding (eg, < 1 cm from the hepatic capsule)

107 Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

108 Life expectancy ≥ 5 months

109 Adequate organ function determined within 4 weeks prior to enrollment, defined as follows:

Hematological

- ANC ≥ 1500/mm^3 (1.5 x 10^9/L) without granulocyte colony-stimulating factor support within 2 weeks prior to enrollment
- white blood cell counts (WBC) > 2500/µL(2.5 x 10^9/L)
- lymphocyte count ≥ 500/µL (0.5 x 10^9/L)
- platelet count ≥ 100,000/mm^3 (100.0 x 10^9/L)
- hemoglobin ≥ 9 g/dL (90 g/L) (without need for hematopoietic growth factor or transfusion support within 2 weeks prior to enrollment)

Renal

- serum creatinine ≤ 1.5 x upper limit of normal (ULN), OR creatinine clearance ≥ 60 mL/min for a subject with serum creatinine levels > 1.5 x ULN. (Note creatinine clearance need not be determined if the baseline serum creatinine is ≤ 1.5 x ULN. Creatinine clearance should be determined per institutional standards).

Hepatic

- serum albumin ≥ 2.5 g/dL (25 g/L)
- serum total bilirubin ≤ 1.5 x ULN
- aspartate aminotransferase (AST) ≤ 2.5 x ULN
- alanine aminotransferase (ALT) ≤ 2.5 x ULN
- alkaline phosphatase (ALP) ≤ 2.5 x ULN

Coagulation

- prothrombin time (PT) or international normalization ratio (INR) ≤ 1.5 x ULN
- partial thromboplastin time (PTT) or activated PTT (aPTT) ≤ 1.5 x ULN

110 Female subjects of childbearing potential should have a negative serum pregnancy test within 1 week prior to enrollment.

4.2 Exclusion Criteria

Cancer Related

201 Subject is a candidate for any hepatic surgery or locoregional therapy of liver metastases with curative intent

202 Approximately more than one-third of the liver estimated to be involved with metastases

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

204 Currently receiving, or < 4 weeks prior to enrollment since receiving liver metastatic-directed therapy (eg, radiation, ablation, embolization) or hepatic surgery

205 History of other malignancy within the past 5 years prior to enrollment with the following exceptions:

- malignancy treated with curative intent and with no known active disease present for ≤ 5 years before enrollment and felt to be at low risk for recurrence by the treating physician and approved by the Amgen medical monitor
- adequately treated non-melanoma skin cancer without evidence of disease at the time of enrollment
- adequately treated cervical carcinoma in situ without evidence of disease at the time of enrollment
- adequately treated breast ductal carcinoma in situ without evidence of disease at the time of enrollment
- prostatic intraepithelial neoplasia without evidence of prostate cancer at the time of enrollment
- adequately treated superficial or in-situ carcinoma of the bladder without evidence of disease at the time of enrollment
- adequately treated superficial or in-situ colorectal carcinoma without evidence of disease at the time of enrollment

206 Active or untreated central nervous system (CNS) metastases. CT or MRI evaluation required during screening for all triple negative breast cancer subjects.

Brain imaging is only required for colorectal cancer subjects with signs or symptoms concerning for CNS metastases or with a history of previously treated CNS metastases.

Subjects with previously treated CNS metastases may participate provided they are stable (no evidence of progression by imaging or requirement for corticosteroids for at least 8 weeks prior to the first dose of investigational product(s) and no ongoing neurologic symptoms). Subjects with a history of treated CNS metastases are eligible, provided they meet the following criteria:

- No metastases to midbrain, pons, or medulla
- No history of intracranial or spinal cord hemorrhage

Note: anticonvulsant prophylaxis (eg, phenytoin, carbamazepine) is permitted

207 History or known presence of leptomeningeal disease

208 Spinal cord compression not definitively treated with surgery and/or radiation or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for ≥ 8 weeks prior to enrollment without ongoing requirement for corticosteroids

209 Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)

Other Medical Conditions

210 History of active autoimmune disease including, but not limited to systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Bell's palsy, Guillain Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis

Note: Subjects with controlled autoimmune thyroid disease, type 1 diabetes mellitus on a stable insulin regimen or vitiligo may be eligible following consultation with the Amgen medical monitor.

211 History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (ie, bronchiolitis obliterans, cryptogenic organizing pneumonia), risk of pulmonary toxicity, or evidence of active pneumonitis on screening chest CT scan

Note: History of radiation pneumonitis in the radiation field (fibrosis) is permitted if there is no ongoing requirement for corticosteroids

212 Evidence of clinically significant immunosuppression such as primary immunodeficiency state such as Severe Combined Immunodeficiency Disease

213 Prior allogeneic bone marrow transplantation or prior solid organ transplantation

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

215 Acute or chronic active hepatitis B infection

216 Acute or chronic active hepatitis C infection

217 Positive test for human immunodeficiency virus (HIV) infection

218 Active tuberculosis

219 Severe infections within 4 weeks prior to enrollment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia and/or received therapeutic oral or intravenous antibiotics within 2 weeks prior to enrollment

Note: Subjects receiving prophylactic antibiotics (eg, for prevention of a urinary tract infection or chronic obstructive pulmonary disease) are eligible

220 Signs or symptoms of infection within 2 weeks prior to enrollment

221 Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction ≤ 3 months prior to the first dose of investigational product(s), unstable arrhythmias, or unstable angina

222 History or evidence of 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 study evaluation, procedures, or completion

223 Female subject is pregnant or breast-feeding, or planning to become pregnant during study treatment and through 5 months after the last dose of talimogene laherparepvec or atezolizumab

224 Female subject of childbearing potential who is unwilling to use acceptable method(s) of effective contraception during study treatment and through 5 months after the last dose of talimogene laherparepvec or atezolizumab. Refer to Section 6.10 for additional contraceptive information.

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

226 Subject who is unwilling to minimize exposure with his/her blood or other body fluids to individuals who are at higher risks for HSV-1 induced complications such as immunosuppressed individuals, individuals known to have HIV infection, pregnant women, or children under the age of 1 year, during talimogene laherparepvec treatment and through 30 days after the last dose of talimogene laherparepvec

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

Exclusions Related to Medications

228 Prior therapy with talimogene laherparepvec, any other oncolytic virus, immune checkpoint inhibitor or immunostimulatory agent

229 Known sensitivity to talimogene laherparepvec or components to be administered during dosing

230 Requires intermittent or chronic treatment with an antiherpetic drug (eg, acyclovir), or other antiviral medication, other than intermittent topical use.

231 History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins

232 Known hypersensitivity or allergy to Chinese hamster ovary cell products or any component of the atezolizumab formulation

233 Prior chemotherapy, targeted therapy (eg, bevacizumab), radiotherapy, to treat cancer or major surgery within 4 weeks prior to enrollment. Subjects who continue to experience > grade 1 Common Terminology Criteria for Adverse Events (CTCAE) toxicity due to cancer therapy within 4 weeks prior to enrollment will not be eligible.

Note: Subjects with ≤ Grade 2 neuropathy and alopecia are an exception to this criterion

234 Currently using an investigational device or receiving treatment with an investigational drug in another study, or less than 4 weeks since ending a study involving an investigational device or investigational drug(s)

235 Treatment with systemic immunosuppressive medications (including but not limited to prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [anti-TNF] agents) within 2 weeks prior to enrollment

- Subject who has received acute and/or low-dose systemic immunosuppressant medications 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.
- The use of inhaled corticosteroids and mineralocorticoids (eg, fludrocortisone) is allowed.

Note: Replacement corticosteroid replacement therapy for adrenal or pituitary insufficiency is not considered a form of systemic immunosuppressive medication

236 Treatment with systemic immunostimulatory agents (including but not limited to interleukin-2) within 4 weeks or five half-lives of the drug, whichever is shorter, prior to enrollment

237 Administration of a non-cancer, live, attenuated vaccine within 4 weeks of enrollment or anticipation that such a live attenuated vaccine will be required during the study or 5 months after the last dose of atezolizumab

238 Requires 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 as long as the institutional guidelines requiring their withholding for interventional radiology procedures can be followed.

5. SUBJECT ENROLLMENT

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

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria. The investigator is to document this decision and date, in the subject's medical record and in/on the enrollment case report form (CRF).

Each subject who enters into the screening period for the study (defined when the subject signs the informed consent) receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned by the Interactive voice/web response system (IxRS). This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject. Subjects who are determined not eligible after screening must be screen-failed in the IxRS system and the reason for the screen-failure provided. Subjects who do not meet all eligibility criteria may be rescreened 1 time at the discretion of the investigator. If a subject is being rescreened, he or she may need to reconsent to the study to ensure that the IRB/IEC approved main informed consent form is signed within 4 weeks prior to enrollment. Subjects may only be enrolled once into this study.

The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened.

5.1 Treatment Assignment

All subjects enrolled will receive open-label talimogene laherparepvec and atezolizumab. 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(s) and/or Medical Device(s)

The Amgen Investigational Product used in this study includes: talimogene laherparepvec.

The Non-Amgen Investigational Product used in this study includes: atezolizumab.

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

6.2 Investigational Product

6.2.1 Amgen Investigational Product: 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 vial with a gray Fluorotec®-coated chlorobutyl elastomer stopper, aluminum seal, and polypropylene cap. Each vial contains a minimum of 1.0 mL talimogene laherparepvec at either 10^6 PFU/mL or 10^8 PFU/mL concentrations. The supply for the 10^6 PFU/mL concentration will be packaged separately from the supply for the 10^8 PFU/mL concentration.

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 (Appendix A). Hematology, chemistry and coagulation panels should be obtained according to the Schedule of Assessments (Table 7-1) and the results should be checked before each treatment administration. Dosing will occur only if these test values are acceptable, per Section 6.2.2.2.

Talimogene laherparepvec will be administered by image guided injection (either ultrasound or CT) into injectable liver lesions. The first cycle of talimogene laherparepvec will be 21 (+ 3) days. Subsequent cycles of talimogene laherparepvec will be 21(+/- 3 days). On cycle 1, day 1, the first dose of talimogene laherparepvec will be up to 4.0 mL of 10^6 PFU/mL. During the second cycle, talimogene laherparepvec will be administered up to 4.0 mL of 10^8 PFU/mL at week 4 of the study (± 3 days). During subsequent cycles, talimogene laherparepvec will be administered up to 4.0 mL of 10^8 PFU/mL every 21 days (± 3 days) thereafter.

The maximum volume of talimogene laherparepvec to be administered at any treatment visit is 4.0 mL for any individual tumor lesion or for all tumor lesions combined. Investigators are encouraged to use the maximum amount when tumor lesions allow.

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 6-1.

Lesions With a Necrotic Core

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 6-1). 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 ultrasound or CT in preparation for injection guidance of each treatment should be used to determine the maximum injection volumes as described in Table 6-1. Talimogene laherparepvec should be injected into viable tissue and direct injection into necrotic tumor tissue should be avoided. 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 6-1. Talimogene Laherparepvec Injection Volume Guideline

Individual Tumor Diameter[a]		
< 75% tumor diameter necrotic[b]	≥ 75% tumor diameter necrotic[b]	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

[a] Longest tumor diameter assessed by ultrasound or CT in preparation for injection guidance.
[b] Based on longest necrotic core diameter divided by longest tumor diameter from most recent multiphase computerized tomography (CT) or magnetic resonance imaging (MRI)

Liver lesions < 1 cm from the hepatic capsule (bleeding risk) or the right main, left main, or common hepatic bile ducts (biliary obstruction risk) should not be injected.

When biopsies of metastatic liver lesions are scheduled on treatment days (Table 7-1), they should be performed prior to intrahepatic administration of talimogene

laherparepvec. Only metastatic liver lesions that have been visualized on screening CT or MRI multiphase scans used for tumor assessments should be injected prior to the first on study radiographic assessment at week 10 (cycle 4).

New liver lesions that have been identified on injection guidance CT scans or ultrasound between scheduled tumor assessments should not be treated with talimogene laherparepvec until they have been visualized on tumor assessment CT or MRI scans and documented in the CRF.

After the first radiographic assessment at week 10 (cycle 4), if all injectable liver lesions have been injected**,** but the 4.0 mL maximum volume has not been used, injection of clinically assessed non-hepatic cutaneous, subcutaneous, and nodal tumor lesions with or without ultrasound guidance will be permitted. Liver lesions should be prioritized over cutaneous, subcutaneous and nodal lesions.

After the initial 6 intrahepatic cycles, there is an option to continue treatment with talimogene laherparepvec for an additional 6 cycles. During this additional dosing period (week 19 [cycle 7] to week 34 [cycle 12]), talimogene laherparepvec may be administered, by intralesional injection to liver metastases or cutaneous, subcutaneous and nodal tumor lesions, or both. For weeks 19 to 34 (cycles 7 to 12), liver lesions do not need to be prioritized. A maximum of 12 cycles (34 weeks) of talimogene laherparepvec are allowed during the study.

The longest diameters of tumors assessed on the day of each treatment should be used to determine the maximum injection volumes per **Table 6-2** for cutaneous, subcutaneous and nodal tumor lesions.

Table 6-2. Talimogene Laherparepvec Injection Volume Guideline Based on Tumor Size for Cutaneous, Subcutaneous, and Nodal Lesions

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

Prioritization for the first 6 cycles (16 weeks) of talimogene laherparepvec is as follows:

- Any new injectable metastatic liver lesion that has appeared on tumor assessment CT or MRI scans since the start of treatment (from newest to oldest).
- Metastatic liver lesions by tumor size, beginning with the largest tumor.
- Any metastatic liver lesion seen on tumor assessment that was previously too small to inject that has now become large enough to inject.
- Injection of non-hepatic lesions (cutaneous, subcutaneous, and nodal tumor lesions) is allowed after the first radiographic assessment at week 10 (ie, after 3 doses) if volume remains after injecting liver lesions.
- After the first 6 cycles (16 weeks), liver lesions do not need to be prioritized.

It is recommended that each metastatic lesion should receive the maximum volume of talimogene laherparepvec possible to inject based on tumor properties at each visit before moving on to the next lesion, using the prioritization model above and injection volume guideline based on the size of the tumor lesion.

Volumes of less than 0.05 mL should not be planned for administration into a tumor lesion. Tumor lesions should be injected until the maximum volume per treatment day (4 mL) has been reached, or there are no further injectable tumor lesions, whichever comes first.

The dose, start date, number of vials used per visit, **concentration,** and lot number of talimogene laherparepvec are to be recorded on each subject's CRF.

Subjects will undergo a 23-hour observation period following the first 3 doses of talimogene laherparepvec treatment with vital signs recorded every 30 minutes for the first 2 hours, hourly for the next 4 hours, then once every 4 to 6 hours. Vital signs should also be recorded at the end of the observation period. The observation period for the fourth dose and subsequent doses 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 observed for a longer duration or hospitalized, if needed, if there is clinical deterioration during the observation period.

When possible, it is preferred that atezolizumab be administered prior to talimogene laherparepvec. Talimogene laherparepvec should be administered within 23 hours of atezolizumab administration. If atezolizumab is administered after talimogene laherparepvec, it should not be administered until the talimogene laherparepvec observation period has ended.

Talimogene laherparepvec will be discontinued if a subject experiences a DLT (during the DLT evaluation period), achieves CR, has no injectable tumor lesions, has confirmed PD per modified irRC-RECIST, needs alternative anticancer therapy, experiences an adverse event necessitating drug discontinuation, or if the investigator determines it is in the best interest of the subject to discontinue treatment due to rapid clinical deterioration, whichever occurs first.

Due to the mechanism of action of immunotherapeutic agents, subjects may experience growth in existing tumors or the appearance of new tumors prior to maximal clinical benefit. Therefore, talimogene laherparepvec dosing should continue, up to a maximum of 12 doses, provided that the subject has no evidence of confirmed PD per modified irRC-RECIST and is able to tolerate treatment.

6.2.1.2 DLT

6.2.1.2.1 DLT Evaluation Period

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 atezolizumab and 3 weeks following the initial 10^8 PFU/mL dose of talimogene laherparepvec and atezolizumab or the start of cycle 3, whichever occurs first. To be evaluable for a DLT, subjects must have had the opportunity to be on treatment for at least 2 cycles from initial dose of study treatments and have received at least 2 doses of talimogene laherparepvec and two doses of atezolizumab in combination, or have a DLT during the DLT evaluation period after at least 1 dose of talimogene laherparepvec and atezolizumab in combination.

6.2.1.2.2 DLRT

A DLRT composed of the investigator(s), Amgen medical monitor, Genentech representative, Amgen Global Safety Officer or designated safety scientist, Amgen Global Clinical Trial Manager and Amgen Biostatistics representative will review data and monitor safety, and make dose decisions (see Section 10.3.2).

6.2.1.2.3 Definition of DLT

All toxicities will be graded using the CTCAE version 4.0 (see Appendix A).

The occurrence of any of the following toxicities during the DLT evaluation period (see Section 3.1) will be considered a DLT, if judged by the investigator to be related to the administration of talimogene laherparepvec or atezolizumab:

- Grade ≥ 4 neutropenia (ANC < 500/μL) lasting ≥ 7 days
- Grade ≥ 3 febrile neutropenia
- Grade ≥ 4 thrombocytopenia
- Grade ≥ 4 anemia
- Grade ≥ 4 rash
- Serious herpetic events (eg, herpetic encephalitis, or disseminated herpetic infection)
- Grade ≥ 3 symptomatic hepatic toxicities that do not resolve to Grade ≤ 2 within 48 hours or Grade ≥ 3 asymptomatic hepatic toxicities that do not resolve to Grade ≤ 1 within 3 weeks of onset with the following exception:
    - Asymptomatic grade 3 laboratory abnormality deemed clinically not significant by both the investigator and Amgen Medical Monitor will not be considered a DLT.
- Grade ≥ 3 non-hematologic, non-hepatic organ toxicity, excluding the following:
    - Grade 3 immune-related adverse event that resolves to Grade ≤ 1 with immunosuppressant therapy within 3 weeks of its onset
    - Grade 3 nausea or vomiting that resolves to Grade ≤ 1 within 72 hours of appropriate supportive therapy
    - Grade ≥ 3 fatigue that resolves to Grade ≤ 2 within 7 days
    - Grade 3 arthralgia that can be adequately managed with supportive care or that resolves to Grade ≤ 2 within 7 days
    - Grade 3 fever (in the absence of any clinically significant source of fever) that resolves to Grade ≤ 2 within 7 days with supportive care
    - Grade ≥ 3 laboratory abnormality that is asymptomatic and deemed by both the investigator and sponsor not to be clinically significant
    - Grade 3 autoimmune thyroiditis or other endocrine abnormality that can be managed by endocrine therapy or hormonal replacement
    - Grade 3 tumor flare defined as local pain, irritation, or rash localized at sites of known or suspected tumor
    - Grade 3 infusion reaction that resolves within 6 hours to Grade ≤ 1
- Grade 5 toxicity (ie, death)
- Any other intolerable toxicity leading to permanent discontinuation of talimogene laherparepvec or atezolizumab

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

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

Dose reduction for adverse events is not allowed. However, if during the process of administering talimogene laherparepvec in the clinic, the subject cannot tolerate the full dose due to an injection-related adverse event such as pain, the total volume given should be recorded, and the reason for intolerance should be documented as an adverse event.

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

- grade 2 or greater immune-mediated adverse events, with the exception of vitiligo
- grade 2 or greater allergic reactions (Note: a grade ≥ 4 rash is considered a DLT if it occurs during the DLT evaluation window and requires permanent discontinuation per Section 6.2.1.2.3)
- any other grade 3 or greater hematologic or non-hematologic toxicity unless deemed not clinically important per both investigator and sponsor. For hepatotoxicity stopping and rechallenge rules see Section 6.4.

For subjects that have an INR of > 1.5 or platelet < 50,000/mm^3 (10^9/L) prior to injection, talimogene laherparepvec administration should be delayed until INR is ≤ 1.5 or platelet ≥ 50,000/mm^3 (10^9/L) without transfusion. Any planned correction of INR or platelet count with transfusion prior to injection should be approved by the Amgen medical monitor.

If a subject requires corticosteroid dosing of >10 mg prednisone daily (or equivalent), for treatment of atezolizumab adverse events or other reason, talimogene laherparepvec dosing must be withheld until the corticosteroid dose has decreased to ≤ 10 mg prednisone daily (or equivalent).

If subject requires tumor necrosis factor alpha (TNF-α) inhibitors for treatment of atezolizumab immune related adverse events, talimogene laherparepvec must be withheld until TNF-α inhibitors are discontinued.

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 either atezolizumab or talimogene laherparpevec is delayed due to toxicity, the cycle must be delayed until both investigational products can be administered safely in

combination. If either atezolizumab or talimogene laherparpevec requires a delay of more than 2 cycles (ie, 6 weeks) because of drug toxicity, that agent should be permanently discontinued (see Section 6.2.2.2 dosage adjustments and delays for atezolizumab).

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 withheld by > 2 cycles (ie, 6 weeks) (ie, approximately 9 weeks from the previous cycle) for reasons other than talimogene laherparepvec related adverse event (eg, delay due to necessitation of corticosteroids for management of atezolizumab adverse event), the investigator must contact the Amgen medical monitor, to determine if the subject can resume talimogene laherparepvec therapy without compromising the subject's safety.

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

- Subject developed a DLT during the DLT evaluation period.
- Possible DILI requiring permanent withholding of talimogene laherparepvec as per Section 6.4.
- The subject, for any reason, requires treatment with alternative anti-cancer agent. In this case, discontinuation from investigational product(s) should occur immediately upon introduction of the new agent.
- Confirmed PD occurs as defined per modified irRC-RECIST.
- 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 2 cycles (ie, 6 weeks) from the date of the planned dose (ie, approximately 9 weeks from the previous cycle).

  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 2 cycles (ie, 6 weeks) from the date of the planned dose (ie, approximately 9 weeks from the previous cycle).

- 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, at the discretion of the investigator, the subject develops clinical evidence of any serious herpes infection (such as, herpetic encephalitis or disseminated infection). Systemic anti-herpetic drugs (eg, acyclovir, valacyclovir, or famciclovir) should only be reserved for suspected cases of severe herpetic infection. Topically administered anti-herpetic drugs may be used for limited suspected herpetic skin lesions after they are swabbed and tested for talimogene laherparepvec DNA using real time polymerase chain reaction (qPCR).

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 30 [+ 7] days after the last dose of talimogene laherparepvec or atezolizumab, whichever is later) and long-term follow-up.

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

6.2.2 Non-Amgen Investigational Product: Atezolizumab

The atezolizumab drug product is provided in a single-use, 20-cc United States Pharmacopeia (USP)/European Pharmacopoeia (Ph. Eur.) Type 1 glass vial as a colorless-to-slightly-yellow, sterile, preservative-free clear liquid solution intended for intravenous administration. The vial is designed to deliver 20 mL (1200 mg) of atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 20 mL volume. The atezolizumab drug product is formulated as 60 mg/mL atezolizumab in 20 mM histidine acetate, 120 mM sucrose, 0.04% polysorbate 20, pH 5.8. Atezolizumab must be refrigerated at 2°C to 8°C (36°F to 46°F) upon receipt until use. Atezolizumab vials should not be used beyond the expiration date provided by the manufacturer. No preservative is used in atezolizumab drug product; therefore, the vial is intended for single use only. Discard any unused portion of drug left in a vial. Vial contents should not be frozen or shaken and should be protected from direct sunlight.

6.2.2.1 Dosage, Administration, and Schedule

Administration of atezolizumab will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies. **Atezolizumab is preferred to be given prior to talimogene laherparepvec.**

The first cycle of atezolizumab will be 21 (+ 3) days. Subsequent cycles of atezolizumab will be 21 (± 3) days. The dose level of atezolizumab is 1200 mg administered by intravenous infusion. In the absence of confirmed PD per **modified** irRC-RE**C**IST, atezolizumab treatment can continue after talimogene laherparepvec treatment has ended provided patient is tolerating atezolizumab and receiving clinical benefit in the opinion of the investigator.

The initial dose of atezolizumab (day 1, cycle 1) will be delivered over 60 (± 15) minutes. If the first dose is tolerated without infusion-associated adverse events, the second dose (cycle 2) may be delivered over 30 (± 10) minutes. If the 30-minute intravenous infusion is well tolerated, all subsequent doses may be delivered over 30 (± 10) minutes. The subjects' vital signs (heart rate, respiratory rate, blood pressure, and temperature) should be determined up to 60 minutes before each atezolizumab intravenous infusion. Vital signs should also be obtained during or after the atezolizumab intravenous infusion if clinically indicated.

No premedication will be allowed for the first dose of atezolizumab. Premedication per Section 6.5 may be administered for subsequent doses at the discretion of the investigator and should be documented in the CRF.

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

There will be no dose reduction for atezolizumab in this study.

If either atezolizumab or talimogene laherparepvec is delayed due to toxicity, the treatment cycle must be delayed until both investigational products can be administered safely in combination. If either atezolizumab or talimogene laherparepvec requires a delay of more than 2 cycles (ie, 6 weeks), because of drug toxicity, that agent should be permanently discontinued.

Dose interruptions for reason(s) other than toxicity, such as surgical procedures, may be allowed with Amgen medical monitor approval. The acceptable length of interruption will depend on agreement between the investigator and the Amgen medical monitor.

Subjects must permanently discontinue atezolizumab treatment if they experience any of the following:

- Symptomatic deterioration attributed to disease progression as determined by the investigator after integrated assessment of radiographic data, biopsy results, and clinical status as applicable
- Intolerable toxicity related to study treatment, including development of an immune related adverse event determined by the investigator and Amgen medical monitor to be unacceptable given the individual subject's potential response to therapy and severity of the event
- Any medical condition that may jeopardize the subject's safety if he or she continues on study treatment
- Subject experiences a DLT during the DLT evaluation period
- Use of another non-study anti-cancer therapy

Subjects will be permitted to continue atezolizumab after confirmed progression per modified irRC-RECIST criteria at the discretion of the investigators as long as the following criteria are met and written approval of the Amgen Medical Monitor is obtained:

- Evidence of clinical benefit as assessed by the investigator
- Absence of symptoms and signs (including worsening of laboratory values; eg, new or worsening hypercalcemia) indicating unequivocal progression of disease
- No decline in ECOG performance status that can be attributed to disease progression
- Absence of tumor growth at critical anatomical sites (eg, leptomeningeal disease). If additional tumor growth occurs then it must be managed by study-allowed treatment procedures (refer to Section 6.6)
- Subjects for whom approved therapies exist must re-sign informed consent form to acknowledge deferring these treatment options in favor of continuing study treatment at the time of confirmed progression.

Refer to the Dose Medication Guidelines for Atezolizumab Related Adverse Events in Appendix F and the latest Atezolizumab Investigator's Brochure.

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 atezolizumab immune-related adverse events that are commercially available are not provided or reimbursed by Amgen (except if required by local regulation). The investigator will be responsible for obtaining supplies of these other protocol-required therapies.

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

6.4 Hepatotoxicity Stopping and Rechallenge Rules

Subjects with impaired liver tests (ie, ALP, AST, ALT, total bilirubin and/or international normalized ratio [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 investigational product(s) (talimogene laherparepvec and/or atezolizumab) as specified in the United States Food and Drug Administration Guidance for Industry Drug-Induced Liver Injury [DILI]: Premarketing Clinical Evaluation, July 2009). Immune-mediated hepatitis has been associated with the administration of atezolizumab. In subjects with impaired liver tests, concurrent medications, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate. Imaging of the liver, gall bladder, and biliary tree should be performed to rule out neoplastic or other causes for increasing liver test values. Anti-nuclear antibody, perinuclear anti-neutrophil cytoplasmic antibody, anti-liver kidney microsomal antibodies, and anti-smooth muscle antibody tests should be performed if an autoimmune etiology is considered. Additionally, appropriate biopsies should be performed if appropriate whenever possible. See Table 6-3 and the latest Atezolizumab Investigator's Brochure for management guidelines for subjects who develop impaired liver tests.

Table 6-3. Guidelines for Management of Hepatic Events for Talimogene Laherparepvec and Atezolizumab

Severity (CTCAE v4.0)	Talimogene laherparepvec (withhold if atezolizumab is withheld)	Atezolizumab (withhold if talimogene laherparepvec is withheld)
Grade 1: ALT ≤ 3xULN; AST ≤ 3xULN; Total bilirubin ≤ 1.5xULN; ALP ≤ 2.5xULN.	Continue Monitor liver function tests	Continue Monitor liver function tests
Grade 2: ALT > 3xULN and ≤ 5xULN; AST > 3xULN and ≤ 5xULN; Total bilirubin > 1.5xULN and ≤ 3xULN; ALP > 2.5xULN and ≤ 5xULN.	Continue Close observation of liver function tests (see Appendix A), check liver function tests prior to next dose. Permanently discontinue, if: AST or ALT > 3xULN; and Total bilirubin > 2xULN; and No other cause for the combination of laboratory abnormalities is immediately apparent (see Section 6.4.1).	Continue if < 5 days duration Close observation of liver function tests (see Appendix A), check liver function test prior to next dose. Withhold for up to 12 weeks after event onset if > 5 days duration. Initiate treatment with 1-2 mg/kg/day IV methylprednisolone, oral prednisone, or equivalent if deemed related to atezolizumab. Resume when liver function tests back to grade 1 or better within 12 weeks. If steroids have been initiated, they must be tapered to < 10 mg daily of prednisone or equivalent before atezolizumab can be resumed. Permanently discontinue if the abnormal liver function test does not resolve to grade 1 or better within 12 weeks, or if: AST or ALT > 3xULN; and Total bilirubin > 2xULN; and No other cause for the combination of laboratory abnormalities is immediately apparent (see Section 6.4.1).

Footnotes defined on last page of the table

Table 6-3. Guidelines for Management of Hepatic Events for Talimogene Laherparepvec and Atezolizumab

Severity (CTCAE v4.0)	Talimogene laherparepvec	Atezolizumab
Grade 3: ALT > 5xULN and ≤ 20xULN; AST > 5xULN and ≤ 20xULN; Total bilirubin > 3xULN and ≤ 10xULN; ALP > 5xULN and ≤ 20xULN.	Withhold if AST or ALT > 5xULN for ≥ 2 weeks; or if AST or ALT > 5xULN and unable to adhere to enhanced monitoring schedule according to Appendix A, or if AST or ALT > 8xULN; or if Total bilirubin > 3xULN; or if ALP > 8xULN. Close observation of liver function tests (see Appendix A). Rechallenge may be considered if an alternative cause for impaired liver tests is discovered and the laboratory abnormalities resolve to normal/baseline. If signs/symptoms recur with rechallenge, permanent discontinuation.	Permanently discontinue* Should be followed according to recommendations in Appendix A Consider starting therapy with 1 to 2 mg/kg/day IV methylprednisolone, oral prednisone, or equivalent; if liver function tests do not decrease within 48 hours of initiating systemic steroids, addition of an alternative immunosuppressive agent may be considered. Taper steroids ≥ 1 month, when symptoms improve to G0/G1 *Resumption of atezolizumab may be considered in subjects who are deriving benefit and fully recovered from event. Patient can be rechallenged only after discussion with and agreement of Amgen Medical Monitor.
Grade 4: ALT > 20xULN; AST > 20xULN; Total bilirubin > 10xULN; ALP > 20xULN.	Permanently discontinue Contact Amgen Medical Monitor	Permanently discontinue Contact Amgen Medical Monitor

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ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; TNF-α = tumor necrosis factor α; ULN = upper limit of normal

6.4.1 Criteria for Permanent Discontinuation of Talimogene Laherparepvec and/or Atezolizumab Due to Potential Hepatotoxicity

Talimogene laherparepvec and/or atezolizumab, should be discontinued permanently and the subject should be followed according to the recommendations in Appendix A (Additional Safety Assessment Information and Drug-induced Liver Injury Reporting & Additional Assessments) for possible DILI, if ALL of the criteria below are met:

- Current total bilirubin > 2x ULN following baseline total bilirubin < 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; important alternative causes for elevated AST/ALT and/or total bilirubin values include, but are not limited to:
  - Hepatobiliary tract disease
  - Viral hepatitis (eg, Hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, Herpes Simplex Virus, 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
  - Non-hepatic causes (eg, rhabdomylosis, hemolysis)

If an alternative cause for hepatotoxicity is identified or less stringent conditions developed than what are noted above, determine (based on patient population and/or severity of the hepatotoxicity or event) if talimogene laherparepvec and/or atezolizumab should be withheld or permanently discontinued, as deemed appropriate for the safety of the subject.

6.4.2 Criteria for Conditional Withholding of Talimogene Laherparepvec and/or Atezolizumab Due to Potential Hepatotoxicity

For subjects who do not meet the criteria for permanent discontinuation of talimogene laherparepvec outlined above and have no underlying liver disease, and eligibility criteria requiring normal transaminases and total bilirubin at baseline or subjects with underlying

liver disease and baseline abnormal transaminases, the following rules are recommended for withholding of Amgen investigational product:

- 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: total bilirubin > 3x ULN at any time
- OR: ALP > 8x ULN at any time

Talimogene laherparepvec and atezolizumab should be withheld pending investigation into alternative causes of DILI. If investigational product(s) is/are withheld, the subject is to be followed according to recommendations in Appendix A for possible DILI. Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP and/or elevated total bilirubin), is discovered and the laboratory abnormalities resolve to normal or baseline (Section 6.4.3).

6.4.3 Criteria for Rechallenge of Talimogene Laherparepvec and/or Atezolizumab After Potential Hepatotoxicity

The decision to rechallenge the subject should be discussed and agreed upon unanimously by the investigator and Amgen medical monitor and between the investigator and patient.

If signs or symptoms recur with rechallenge, then talimogene laherparepvec and/or atezolizumab should be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Section 6.4.1) should never be rechallenged without discussing with the Amgen 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.

Subjects who experience atezolizumab infusion-associated symptoms may be treated symptomatically with acetaminophen, diphenhydramine, and/or famotidine or another H2 receptor antagonist, as per standard practice (for sites outside the United States, equivalent medications may be substituted per local practice). Serious atezolizumab related infusion associated events manifested by dyspnea, hypotension, wheezing,

bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (eg, supplemental oxygen and β2-adrenergic agonists).

Systemic corticosteroids and TNF-α inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab but may be administered at the discretion of the treating physician after consultation with the Amgen medical monitor. If corticosteroids (prednisone > 10 mg or equivalent **daily**) or TNF-α inhibitors are needed for treatment of atezolizumab immune related adverse events, talimogene laherparepvec must be withheld until the corticosteroid dose is ≤ 10 mg prednisone or equivalent **daily** or TNF-α inhibitors are discontinued (see Section 6.2.1.3). If feasible, alternatives to corticosteroids should be considered.

Premedication may be administered for the second and all subsequent doses of atezolizumab at the discretion of the treating physician (see Section 6.2.2.1) The use of inhaled corticosteroids and mineralocorticoids (eg, fludrocortisone) for subjects with orthostatic hypotension or adrenocortical insufficiency is allowed.

Inactivated influenza vaccination may be given but only during influenza season. However, subjects must not receive live, attenuated influenza vaccine (eg, FluMist®) within 4 weeks prior to the first dose of talimogene laherparepvec and atezolizumab (day 1) or at any time during the study and an additional 5 months after the last dose of talimogen**e** laherparepvec or atezolizumab, whichever is later.

All concomitant therapies are to be collected in the CRF from informed consent through 30 (+ 7) days after the last dose of talimogene laherparepvec or atezolizumab**,** whichever comes later.

For concomitant therapies collect therapy name, indication, dose, unit, frequency, route, start date, and stop date.

6.6 Other Treatment Procedures

Local radiation treatment to the site of bone and other metastasis will be permitted for palliative pain management at any time during the study. Subjects with local symptoms suggestive of disease progression should undergo tumor assessment prior to the administration of palliative radiotherapy. If a subject undergoes local radiation, study treatment should be withheld, and the investigator or designee should notify the Amgen medical monitor.

If a subject demonstrates evidence of new or worsening CNS metastases, all study treatments should be withheld. After discussion between the Amgen medical monitor and the investigator to determine the appropriateness of treatment resumption provided CNS metastases are adequately treated, subjects may be allowed to remain on study. In addition, in order to resume talimogene laherparepvec or atezolizumab, corticosteroid dose must not exceed 10 mg of prednisone or equivalent **daily**. Re-exposure to talimogene laherparepvec and atezolizumab may occur only if the investigator and sponsor agree that the subject safety will not be compromised.

6.7 Medical Devices

Medical devices (eg, syringes, sterile needles, alcohol prep pads) that are commercially available are not usually provided or reimbursed by the Sponsor (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 a drug(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.

This includes any drug(s) or device(s) provisioned and/or repackaged/modified by Amgen. Drug(s) or device(s) includes investigational product.

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

6.9 Excluded Treatments, Medical Devices, and/or Procedures During Study Period

Subjects must not use any of the following therapies during treatment period:

- other investigational agents or procedures
- concurrent experimental or approved antitumor therapies other than protocol specified therapies and radiation therapy required for symptom palliation.
- immunosuppressive agents with the exception of treatment for adverse events
    - If the subject requires corticosteroid dosing for related toxicities (eg, prednisone >10 mg or equivalent), talimogene laherparepvec dosing must be withheld until the corticosteroid dose is able to be decreased to **≤** prednisone 10 mg (or equivalent) **daily**.

- Subjects who are receiving talimogene laherparepvec may not receive antiherpetic drugs (eg, acyclovir) with the exception of treatment for adverse events, but may receive a topically administered antiherpetic drug more than 20 cm from a talimogene laherparepvec injection site.
- Subjects who are receiving a nuclear factor-kappa B ligand (RANKL) inhibitor prior to enrollment must be willing and eligible to receive a bisphosphonate instead; RANKL inhibitors could potentially alter the activity and the safety of atezolizumab.
- Immunostimulatory agents not part of study treatment, including but not limited to interferon-gamma or interleukin-2; these agents, in combination with atezolizumab, could potentially increase the risk for autoimmune conditions. In addition, subjects should not receive immunostimulatory agents for 10 weeks after the last dose of atezolizumab.
- azathioprine, methotrexate, and thalidomide; these agents could potentially alter the activity and the safety of atezolizumab. Systemic corticosteroids, TNF-α inhibitors, mycophenolate and other immune suppressants may be administered for the treatment of immune-related toxicities at the discretion of the treating physician after consultation with the Amgen medical monitor.
- 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 treatment. 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 Amgen medical monitor as soon as possible. A subject may be allowed to resume study treatment if both the investigator and Amgen medical monitor agree to restart.

6.10 Contraceptive Requirements

Female of Childbearing Potential

A female is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Female in the following categories are not considered of child bearing potential:

1. Premenopausal female with 1 of the following:
   a. Documented hysterectomy
   b. Documented bilateral salpingectomy
   c. Documented bilateral oophorectomy

   Note: Site personnel documentation from the following sources is acceptable: 1) review of subject medical records, 2) subject medical examination, or 3) subject medical history interview.

2. Premenarchal female

3. Postmenopausal female

   a. 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.

   b. Females on HRT and whose menopausal status is in doubt will be required to use one 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.

6.10.1 Female Subjects

Female subjects of childbearing potential must agree to use one acceptable method of effective contraception (as described in the table below) during treatment and for an additional 5 months after the last dose of talimogene laherparepvec or atezolizumab.

Acceptable Methods of Effective Contraception for Female Subjects
• Combined (estrogen and progestogen) or Progestogen-only hormonal methods given via oral, 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.)

If a female subject is suspected of being pregnant, the protocol-required therapies must be stopped immediately and may not be resumed until absence of pregnancy has been medically confirmed.

6.10.2 Unacceptable Methods of Birth Control for Female Subjects

Birth control methods that are considered unacceptable in clinical trials include: periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method.

Female subjects of childbearing potential must receive pregnancy prevention counseling and be advised of the risk to fetus if they become pregnant during treatment and for 5 months after the last dose of talimogene laherparepvec or atezolizumab.

7. STUDY PROCEDURES

7.1 Schedule of Assessments

For Schedule of Assessments please refer to Table 7-1.

Table 7-1. Schedule of Assessments

Period	Screening	Treatment [a]													Safety Follow-up[b]	Long-term Follow-up[c]
Cycles		1	2	3	4	5	6	7	8	9	10	11	12	13 and beyond		
Weeks	- 4 weeks	1 (day 1)	4	7	10	13	16	19	22	25	28	31	34	Every 3 weeks after week 34		
General Assessments																
Informed Consent	X															
Demographics	X															
Medical/Surgical History[d]	X															
Physical Exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Weight	X	X													X	
Performance Status: ECOG	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-Lead ECG	X															
Record disease related events, adverse events & serious adverse events[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[c]
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[c]
Survival Assessment																X[c]
Local Laboratory Tests																
Hepatitis B surface antigen and core antibody/Hepatitis C virus antibody	X															
HIV antibody	X															
Serum pregnancy test[g]	X															
Coagulation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Thyroid function (TSH, Free T3 & Free T4[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis	X															

Footnotes defined on next page of table

Table 7-1. Schedule of Assessments

Period	Screening	Treatment [a]													Safety Follow-up[b]	Long-term Follow-up[c]
Cycles		1	2	3	4	5	6	7	8	9	10	11	12	13 and beyond		
Weeks	- 4 weeks	1 (day 1)	4	7	10	13	16	19	22	25	28	31	34	Every 3 weeks after week 34		
Local Laboratory Tests																
Tumor markers (eg. CA 27.29, CA 15-3 or CEA and CA 19-9) as applicable[i]		X			X			X			X			X[n]	X	
Central Laboratory Tests																
Archival tumor sample		X														
HSV-1 serostatus		X		X											X	
Swab for Herpetic tumor for qPCR	Within 3 days of event if applicable															
Liver tumor biopsy[j]		X		X			X									
Blood for biomarker analysis[k]		X	X	X			X								X	
Response Assessments																
Radiographic (CT, PET/CT, or MRI) Scans +/- bone scans[l]	X				X			X			X			X[n]	X[l]	X[l]
Clinical Tumor Assessments[m]	X				X			X			X			X[n]		X
Treatment Administration																
Atezolizumab administration		X	X	X	X	X	X	X	X	X	X	X	X	X		
Talimogene laherparepvec administration[a]		X	X	X	X	X	X	X	X	X	X	X	X			
Reporting Exposure to Talimogene Laherparepvec																
Exposure of Subject's Healthcare Provider		X	X	X	X	X	X	X	X	X	X	X	X	X[o]	X	
Exposure of Subject's Household Member or Caregiver		X	X	X	X	X	X	X	X	X	X	X	X	X[o]	X	

CA 19.9 = cancer antigen 19-9; CA 27.29 = cancer antigen 27.29; CA 15-3 = cancer antigen 15-3; CEA carcinoembryonic antigen; CNS = central nervous system; CT = computerized tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; HIV = human immunodeficiency virus; HSV-1 = herpes simplex virus type 1; irRC-RECIST = immune-related response criteria simulating Response Evaluation Criteria in Solid Tumors; MRI = magnetic resonance imaging; PET = positron emission tomography; qPCR = real-time polymerase chain reaction; TSH = thyroid stimulating hormone; T3 = triiodothyronine;T4 = thyroxine; ULN = upper limit of normal

[a] After the initial 6 intrahepatic cycles of talimogene laherparepvec, there is an option to continue treatment with talimogene laherparepvec for an additional 6 cycles. During this additional dosing period (cycles 7 to 12), talimogene laherparepvec may be administered, by intralesional injection to liver metastases or cutaneous, subcutaneous and nodal tumor lesion, or both. For cycles 7 to 12, liver lesions do not need to be prioritized. A maximum of 12 cycles of talimogene laherparepvec are allowed during the study. In the absence of confirmed PD per **modified** irRC-RECIST, atezolizumab treatment can continue after talimogene laherparepvec treatment has ended provided patient is tolerating atezolizumab and receiving clinical benefit in the opinion of the investigator.

[b] Safety follow-up will be performed approximately 30 (+ 7) days after the last dose of study treatment.

[c] Subjects will be followed for survival every 12 weeks (± 28 days) from the date of the safety follow-up visit until up to approximately 24 months after the last subject is enrolled. Subsequent cancer treatments will be collected as part of the long-term follow-up survival assessment. In addition, talimogene laherparepvec related adverse events that occur after the safety follow-up visit through the end of the long-term follow-up will be reported.

[d] For subjects with metastatic colorectal cancer, if known, KRAS, NRAS, BRAF, and MSI test results (including date of testing and assay used) are to be recorded in a separate eCRF at the time of enrollment or at the subsequent time that the results become available. See Section 7.3.3.

[e] Subjects will undergo a 23-hour observation period following the first 3 doses of talimogene laherparepvec treatment with vital signs recorded every 30 minutes for the first 2 hours, hourly for the next 4 hours, then once every 4 to 6 hours. Vital signs should also be recorded at the end of the observation period. After the fourth dose of talimogene laherparepvec, the observation period for subsequent doses 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' vital signs (heart rate, respiratory rate, blood pressure, and temperature) should be determined up to 60 minutes before each atezolizumab intravenous infusion. Vital signs should also be obtained during or after the atezolizumab intravenous infusion if clinically indicated.

[f] Serious adverse events are reportable 90 days after last treatment dose.

[g] Serum pregnancy test must be done within 1 week prior to enrollment.

[h] 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.

[i] Tumor marker measurement is required to confirm CR if baseline level of tumor marker was above the ULN and criteria for CR per modified irRC-RECIST guidelines are met. Blood samples for tumor biomarkers are to be collected prior to administration of investigational agent/s per Schedule of Assessments. Tumor marker measurements should be performed according to institutional guidelines and availability.

[j] Liver tumor biopsies: 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. During treatment liver tumor biopsies will be performed immediately prior talimogene laherparepvec administration at weeks 1, 7, and 16. Screening biopsy may be used for baseline (week 1) biopsy if the subject is eligible, provided enough tissue has been obtained. One injected lesion should be biopsied at each time point. If there are uninjected lesions that are suitable for biopsy at week 7 and/or week 16, one uninjected lesion should also be biopsied at that time prior to talimogene laherparepvec administration.

[k] Blood will be collected for biomarker analysis prior to any study drug (atezolizumab and talimogene laherparepvec) administration and approximately 4 hours (± 30 minutes) following talimogene laherparepvec administration.

[l] CT/MRI brain required at screening for triple negative breast cancer subjects. An MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal scan. Only colorectal cancer subjects with signs/symptoms for CNS metastases need to have brain imaging. During treatment, radiographic tumor imaging and clinical tumor assessments will be performed independent of treatment cycle at week 10 (± 1 week) and then every 9 weeks (± 1 week) until confirmed disease progression (PD). Of note, atezolizumab is permitted to continue beyond confirmed PD in which case radiographic tumor imaging should continue until the subject discontinues treatment. Radiographic imaging is only required at the safety follow-up visit if subject ended treatment prior to documentation of confirmed PD per modified ir**R**C-RECIST and has not had radiographic tumor imaging performed within 9 (± 1) weeks of the visit and has not started new anti-cancer therapy. In the case that the subject discontinues therapy prior to documentation of confirmed PD per modified irRC-RECIST, every effort should be made to complete radiographic assessments during the long-term follow-up approximately every 12 weeks (+ 28 days) until documented confirmed PD per modified irRC-RECIST, start of new anticancer treatment, death, or end of study, whichever occurs first.

[m] Clinical measurements of cutaneous, subcutaneous, and palpable nodule tumor lesions by caliper should be measured at baseline as well as at subsequent tumor assessments. For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested.
[n] Every 3 cycles (approximately 9 weeks)
[o] Subjects should be monitored for potential exposure cases that occur after the last dose of talimogene laherparepvec through 30 (+ 7) days after the last dose of talimogene laherparepvec.

7.2 General Study Procedures

The procedures performed and timing of each study visit are outlined in the Schedule of Assessments (**Table 7-1**). Details regarding each type of procedure are provided in subsequent subsections. Procedures that are part of routine care are not considered study-specific procedures and may be used at screening to determine eligibility.

Refer to the applicable supplemental central laboratory, IxRS, IPIM, and study manuals for detailed collection and handling procedures.

7.2.1 Screening and Enrollment

Informed consent must be obtained before completing any screening procedure or discontinuation of standard therapy or any disallowed therapy. After signing the written informed consent form, the site will register the subject in IxRS and screen the subject in order to assess eligibility for participation. Screening procedures are to be completed during the screening period within 4 weeks prior to enrollment. If a subject has not met all eligibility criteria at the end of the 4-week window, the subject will be registered as a screen fail. Screen fail subjects may be eligible for re-screening once as described in Section 7.2.2. Prior to enrollment, subject eligibility must be confirmed with screening procedures. Subjects satisfying eligibility requirements will be enrolled. The time points for the procedures to be completed during the screening period are designated in the Schedule of Assessments.

7.2.2 Re-screening

Subjects who are unable to complete or meet eligibility on initial screening will be permitted to re-screen once. Re-screen subjects must first be registered as screen failed in I**x**RS and subsequently registered as re-screened. Subjects will retain the same subject identification number assigned at the original screening. Once the subject is registered as re-screened, a new 4 week screening window will begin. If the re-screening period begins more than 4 weeks after the original signing of the informed consent form, all screening procedures, including informed consent must be repeated. If the re-screening occurs less than 4 weeks after the original signing of the informed consent, then only those criteria that were originally failed are required to be repeated provided the tests that meet criteria fall within the time frame of the screening window.

7.2.3 Treatment

During the treatment period, visits will occur per the Schedule of Assessments (Table 7-1). The date of the first dose of investigational products is defined as day 1

(week 1). All subsequent doses and study visits will be scheduled based on the day 1 date. On-study visits may be completed within ± 3 days of the planned visit date. Investigational product administration should begin as soon as possible after enrollment via IxRS but no later than 5 days after enrollment. Investigational products are to be administered after all other study procedures are completed, during each visit that it is required. 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 specified otherwise.

7.2.4 Follow-up

7.2.4.1 Safety Follow-up

All subjects will complete a safety follow-up visit approximately 30 (+ 7) days after the last dose of study treatment. The time points for the procedures to be completed during the safety follow-up period are designated in the Schedule of Assessments.

7.2.4.2 Long-Term Follow-up

After the safety follow-up visit subjects will enter the long-term follow-up. Subjects will be contacted to assess survival and initiation of additional anticancer therapy.

Contact for all subjects will be attempted every 12 weeks (± 28 days) following the safety follow-up visit until death, subject or legally acceptable representative withdraws full consent/assent, or up to 24 months after the last subject is enrolled, whichever comes first. Anticancer therapies and treatment related adverse events that occur through the end of the long-term follow-up will be reported.

For subjects who discontinued treatment for any reason other than confirmed PD every effort should be made to perform radiographic scans for tumor assessments every 12-weeks (± 28 days) until documentation of confirmed PD per modified irRC-RECIST, start of new anticancer therapy, or end of study, whichever occurs first.

Subjects who are alive at the end of study and received talimogene laherparepvec, will be consented and followed for long term survival and safety on the registry study (see Section 3.1)

7.3 Description of Study Procedures

The sections below provide a description of the individual study procedures for required timepoints.

7.3.1 Informed Consent

All subjects or legally acceptable representative must sign and personally date the IRB/IEC approved informed consent and if required the subject has provided assent before any study specific procedures are performed.

7.3.2 Demographic Data

Demographic data including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness. Additionally**,** demographic data will be used to study the impact of the protocol-required therapy **on biomarkers variability**.

7.3.3 Medical History

The investigator or designee will collect complete medical and surgical history. Medical history will include information on the subject's concurrent medical conditions, clinically significant diseases, surgeries, cancer history (including prior cancer procedures and assessment of tumor mutational status and tumor molecular characteristic), reproductive status, smoking history, use of alcohol and drugs of abuse. For subjects with metastatic colorectal cancer, if known, KRAS, NRAS, BRAF, and MSI test results (including assay used) are to be recorded in a separate eCRF at the time of enrollment or at the subsequent time that the results become available. The current severity will be collected for each condition that has not resolved. Triple negative breast cancer and colorectal cancer history must date back to the original diagnosis. Record all findings on the medical history CRF.

7.3.4 Prior Therapies

Prior therapies (eg, prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) that were being taken from 4 weeks prior to screening through informed consent should be collected.

For prior therapies, therapy name, indication, dose, unit, frequency, and start and stop date will be collected for all prior therapies taken for current or prior malignancies.

7.3.5 Concomitant Therapy

All concomitant medications that are administered after the subject has signed informed consent through 30 (+ 7) days after the last administration of study treatment will be recorded in the CRF (refer to Section 6.5). Concomitant medications should be assessed on an ongoing basis and recorded at each subject visit. Only subsequent anticancer therapy will be recorded during the long-term follow-up period.

7.3.6 Adverse Events, Disease Related Events and Serious Adverse Events

Safety event reporting procedures are described in Section 9.2.

7.3.7 Physical Examination

A physical examination will be performed at screening per standard of care. At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the adverse event CRF. Physical examination findings should be recorded on the appropriate CRF (eg, medical history, event).

7.3.8 Vital Signs

Vital signs (including systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature): Subjects must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The position selected and temperature location 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.

Vital signs should be obtained prior to investigational product administration and if necessary during and after administration of study treatment(Refer to Section 6.2.1.1 and Section 6.2.2.1).

7.3.9 Physical Measurements

Body weight will be recorded in kilograms.

7.3.10 ECG

A 12-lead electrocardiogram (ECG) will be performed per standard of care. 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 ECG must include the following measurements: heart rate, PR interval, QRS, QT and QTc intervals. 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.

7.3.11 ECOG

ECOG performance status will be collected as outlined in Appendix E.

7.3.12 Reporting of Exposure to Talimogene Laherparepvec

If a household member, caregiver, or healthcare provider who has had close contact with a subject treated with talimogene laherparepvec on this study is suspected to have been exposed to talimogene laherparepvec (eg, have or who have had signs or symptoms suspected to be herpetic in origin or who have been accidentally exposed to talimogene laherparepvec), while the subject is taking talimogene laherparepvec, the exposure must be reported to Amgen. Refer to Section 9.4.

7.3.13 Tumor Assessments

7.3.13.1 Clinical Tumor Assessments

Clinical measurements of cutaneous, subcutaneous, and palpable nodal tumor lesions by caliper should be measured at baseline as well as at subsequent tumor assessments. For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested to aid tracking. Photographs are not required for the study; therefore, photographic equipment will not be provided.

Clinically applicable tumor measurements include but are not limited to cancer antigen 27.29 (CA 27.29), cancer antigen 15-3 (CA 15-3), carcinoembryonic antigen (CEA), and cancer antigen 19-9 (CA 19-9). Blood samples for tumor biomarkers are to be collected prior to administration of investigational agent/s per Schedule of Assessments (Table 7-1). Tumor marker measurements should be performed according to institutional guidelines and availability. Tumor marker measurement is required to confirm CR if screening level of tumor marker was above the ULN and criteria for CR per modified irRC-RECIST guidelines are met.

7.3.13.2 Radiographic Tumor Assessment

All known sites of disease must be documented at screening and reassessed at each subsequent tumor evaluation.

Screening assessments must include CT scans (with oral/IV contrast unless contraindicated) or MRI of the chest, abdomen, and pelvis. A spiral CT scan of the chest may be obtained but is not a requirement. An MRI or a non-contrast CT scan of the chest, abdomen, and pelvis may be used in subjects for whom CT scans with contrast are contraindicated (ie, subjects with contrast allergy or impaired renal clearance). If a subject had imaging as part of standard of care, it does not need to be repeated

provided it is of adequate quality as outlined above and falls within the screening window.

A CT (with contrast) or MRI scan of the brain must be done at screening to evaluate CNS metastasis in all subjects with triple negative breast cancer. A brain scan is only required for colorectal cancer subjects if they present with signs/symptoms of CNS metastasis. An MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal scan. Subjects with active or untreated CNS metastases are not eligible for this study.

If a CT scan for tumor assessment is performed in a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards for a full-contrast diagnostic CT scan.

Bone scans should also be performed if clinically indicated. At the investigator's discretion, other methods of assessment of measurable disease as per modified irRC-RECIST may be used (Appendix D).

The same radiographic procedure used to assess disease sites at screening should be used throughout the study (eg, the same contrast protocol for CT scans). All known sites of disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Response will be assessed by the investigator using modified irRC-RECIST criteria (Appendix D). Assessments should be performed by the same evaluator if possible to ensure internal consistency across visits.

7.4 Laboratory Assessments

On-treatment tests can be performed within 3 days of the treatment visit. Results should be reviewed prior to the administration of study treatment. All tests (except for real-time polymerase chain reaction [qPCR], HSV-1 antibody, archival tumor sample, liver tumor biopsy and blood for biomarkers) are to be performed at the local laboratory. Specific analytes for serum chemistry, coagulation, hematology, urinalysis, and other testing to be conducted on blood, urine and swabs are below (**Table 7-2**). During treatment, assessments and procedures can be performed within 3 days of the planned visit unless specified in study procedures.

Table 7-2. Laboratory Analytes

Local Laboratory Serum Chemistry	Local Laboratory Coagulation	Local Laboratory Hematology	Local Laboratory Urinalysis	Other Labs
Sodium	PT or INR	Red blood cell count	Specific gravity	<u>Local Laboratory</u>
Potassium	aPTT or PTT	Hemoglobin	pH	Serum pregnancy test
Chloride		Hematocrit	glucose	Hepatitis B surface antigen and Hepatitis B core antibody
Bicarbonate		Platelets	protein	Hepatitis C virus antibody
Calcium		White blood cell count	ketones	HIV antibody
Magnesium		Differential [a]	blood	Tumor markers CEA, tumor markers (if clinically applicable)
Phosphorus		• ANC		CA 15-3[b]
Total protein		• Eosinophils[d]		CA 27.29[b]
Albumin		• Basophils		CEA & CA 19-9[c]
BUN or Urea		• Lymphocytes		<u>Central Laboratory</u>
Creatinine		• Monocytes		Archival tumor sample
Total bilirubin		• Total neutrophils or segmented neutrophils and bands		qPCR for talimogene laherparepvec DNA
ALP				HSV-1 antibody
AST				Liver tumor biopsy
ALT				Biomarker analysis
Glucose				<u>Biopsy Lab</u>
LDH				PD-L1 & CD8 IHC
TSH				
Free T3				
Free T4				

ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time ;AST = aspartate aminotransferase; ALT = alanine aminotransferase; BUN = blood urea nitrogen; CA 19-9 = cancer antigen 19-9; CA 15-3 = cancer antigen 15-3; CA 27.29 = cancer antigen 27.29; CEA = carcinoembryonic antigen; DNA = deoxyribonucleic acid; free T3=free triiodothyronine; free T4 = free thyroxine; HIV = human immunodeficiency virus; HSV-1 = herpes simplex virus type-1; IHC = immunohistochemistry; INR = international normalization ratio; LDH = lactate dehydrogenase; **PD-L1 = programmed cell death ligand-1;** PT = prothrombin time; qPCR = real-time polymerase chain reaction; TSH = thyroid stimulating hormone

[a] 3-part differential (neutrophils, eosinophils, basophils) acceptable if 5-part unable to be performed

[b] only in subjects with triple negative breast cancer

[c] only in subjects with colorectal cancer

7.4.1 qPCR for Talimogene Laherparepvec

Swab of cold sore, vesicles and other lesions suspected to be herpetic in origin (if any) for qPCR testing of talimogene laherparepvec DNA must be collected. Subject should return to the clinic within 3 days of the occurrence of a reportable lesion suspected to be herpetic in origin. The lesion should be evaluated by the investigator and swabbed if HSV infection is suspected. A qPCR analysis will be performed on the swab sample by the central laboratory to evaluate whether the talimogene laherparepvec DNA is detectable in the sample.

7.5 Biomarker Development

Biomarkers are objectively measured and evaluated indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. In oncology, there is particular interest in the molecular changes underlying the oncogenic processes that may identify cancer subtypes, stage of disease, assess the amount of tumor growth, or predict disease progression, metastasis, and responses to investigational product(s) or protocol-required therapies.

Amgen may attempt to develop test(s) designed to identify subjects most likely to respond positively or negatively to investigational product(s) (eg, Amgen or non-Amgen investigational product or protocol-required therapies).

7.5.1 Blood Samples

Blood samples are to be collected for biomarker development prior to any study drug (atezolizumab and talimogene laherparepvec) administration and approximately 4 hours (± 30 minutes) following talimogene laherparepvec administration per the schedule of assessments at the following time points: at day 1 (week 1), week 4, week 7, week 16, and at the safety follow-up visit (baseline only).

7.5.2 Archival Tumor Samples

For archival tumor samples that should be submitted within the first 4 weeks after enrollment, a block of formalin-fixed paraffin-embedded tumor tissue collected prior to the study is to be sent to the central laboratory along with the corresponding pathology report. The tumor block is to be carefully selected by a pathologist or a skilled experienced histology associate to include generous tumor tissue using the pathology report as a guide. In lieu of a block, approximately 20 unstained sections on charged slides from the same block can be submitted. When the samples of tumor tissues are available, analyses of tumor specific mutations or epigenetic changes may be performed (eg, somatic mutations).

7.5.3 Liver Tumor Biopsies

Liver tumor biopsies 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. A screening biopsy is only required if the subject does not have histologically or cytologically confirmed disease required to confirm eligibility.

One injected lesion should be biopsied at each time point. If there are uninjected lesions that are suitable for biopsy at week 7 and/or week 16, one uninjected lesion should also be biopsied at that time prior to talimogene laherparepvec administration.

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

7.6 Pharmacogenetic Studies

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

7.7 Sample Storage and Destruction

Any blood or tumor sample collected according to the Schedule of Assessments (Table 7-1) 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 or legally acceptable representative, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the cancer, the dose response and/or prediction of response to talimogene laherparepvec and characterize 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 benefit the subject directly or to alter the treatment course, the results of pharmacogenetic or other exploratory studies are not

placed in the subject's medical record and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

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

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample.
See Section 11.3 for subject confidentiality.

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 undergoing 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 7-1), 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 subject 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 7-1**) 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).

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

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

The investigator and/or sponsor can decide to withdraw a subject(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

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

- subject request
- ineligibility determined
- protocol deviation
- non-compliance
- adverse event necessitating drug discontinuation
- other protocol specified criteria (CR, no injectable lesions [talimogene laherparepvec only])
- death
- lost to follow-up

- decision by Sponsor (other than subject request, adverse event necessitating drug discontinuation, lost to follow-up)
- disease progression (confirmed disease progression as per modified irRC-RECIST required for talimogene laherparepvec only unless subject has rapid clinical deterioration requiring withdrawal from treatment)
- pregnancy

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 Disease Related Events

Disease Related Events are events (serious or non-serious) anticipated to occur in the study population due to the underlying disease. **All serious disease related events will be recorded and reported to the sponsor or designee within 24 hours.** 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.

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.

9.1.2 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 adverse events are due to metastatic triple negative breast cancer or colorectal cancer, the primary tumor type (eg, metastatic cancer) 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 Serious Adverse Events

A serious adverse event is defined as an adverse event that meets at least one 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, PD or pain or discomfort caused by growing tumors) 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 patient with the same underlying condition, or
- if the investigator believes a causal relationship exists between the investigational medicinal product(s)/protocol-required therapies and the event
- and the event meets at least one of the serious criteria above

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 (see Appendix A for DILI reporting criteria), or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

9.1.4 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $> 10 \times$ ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, influenza-like illness, systemic inflammatory response syndrome, and systemic immune activation
- Nephritis
- Ocular toxicities (eg, uveitis, retinitis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (eg, atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia

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 atezolizumab through the safety follow-up visit (ie, 30 [+7] days after the last dose of talimogene laherparepvec or atezolizumab), are recorded on the Event CRF as a Disease-Related 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.

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)
- Severity (and/or toxicity per protocol)
- Assessment of relatedness to talimogene laherparepvec and/or atezolizumab and
- Action taken

CTCAE version 4 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.

Disease-Related Events assessed by the investigator to be more severe than expected and/or related to the talimogene laherparepvec or atezolizumab, and determined to be serious, must be recorded on the Event CRF as Serious Adverse Events **and be recorded and reported per Section 9.1.1**.

Additionally, the investigator is required to report a fatal Disease Related Event on the Event CRF.

9.2.2 Adverse Events

9.2.2.1 Reporting Procedures for Adverse Events That Do Not Meet Serious Criteria

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after first dose of talimogene laherparepvec or atezolizumab through the safety follow-up visit (ie, 30 [+7] days after the last dose of talimogene laherparepvec or atezolizumab) are reported using the Event CRF.

Additionally, talimogene laherparepvec or atezolizumab related adverse events that occur after the safety follow-up visit through the end of the long-term follow-up will be reported.

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)
- Severity (and/or toxicity per protocol)
- Assessment of relatedness to talimogene laherparepvec and/or atezolizumab
- Action taken

The adverse event grading scale used will be the CTCAE version 4.0. The grading scale used in this study is described in Appendix A.

The investigator must assess whether the adverse event is possibly related to the talimogene laherparepvec and/or atezolizumab. This relationship is indicated by a “yes” or “no” response to the question: Is there a reasonable possibility that the event may have been caused by the investigational product(s)?

The investigator must assess whether the adverse event is possibly related to any study-mandated activity (eg, administration of investigational product, protocol-required therapies, use of medical device(s) and/or procedure (including any screening procedure(s)). 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 investigational product, protocol-required therapies, use of medical device(s)), 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 changes from the date of onset to the date of resolution, record a single event for each level of severity on the Event CRF.

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

9.2.2.2 Reporting Procedures for Serious Adverse Events and Adverse Events of Special Interest

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through 90 (+ 7) days following cessation of treatment, or if the subject initiates new anticancer therapy, whichever is earlier are recorded in the subject's medical record and are submitted to Amgen. Additionally, talimogene laherparepvec and/or atezolizumab related serious adverse events that occur after the safety follow-up visit through the end of the long-term follow-up will be reported.

All serious adverse events and adverse events of special interest must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the Event 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 an electronic Serious Adverse Event Contingency Report Form within 24 hours of the investigator's knowledge of the event. See Appendix B for a sample of the Serious Adverse Event Worksheet /electronic Serious Adverse Event Contingency Report Form. For EDC studies where the first notification of a Serious Adverse Event is reported to Amgen via the eSerious Adverse Event Contingency Report Form, the data must be entered into the EDC system when the system is available again.

The investigator must assess whether the serious adverse event is possibly related to the investigational product (talimogene laherparepvec and/or atezolizumab), medical devices, combination product(s), and/or other protocol-required therapies. 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 atezolizumab, combination products, and /or other protocol-required therapies? Relatedness means that there are facts or reasons to support a relationship between investigational product and the event.

The investigator is expected to follow reported serious adverse events and adverse events of special interest until stabilization or reversibility.

New information relating to a previously reported serious adverse event or adverse event of special interest must be submitted to Amgen. All new information for serious adverse events or adverse events of special interest must be sent to Amgen within 24 hours following knowledge 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 record. Information provided about the serious adverse event and adverse event of special interest must be consistent with that recorded on the Event CRF.

If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event or adverse event of special interest, 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.

9.2.2.3 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 or after end of study. However, these serious adverse events can be reported to Amgen. In some countries (eg, European Union [EU] member states), investigators are required to report serious adverse events that they become aware of after end of study. If serious adverse events are reported, the investigator is to report them to Amgen within 24 hours following the investigator's knowledge of the event.

Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases for the purposes of expedited reporting.

9.3 Pregnancy and Lactation Reporting

If a female subject becomes pregnant, or a male subject fathers a child, while the subject is taking talimogene laherparepvec or atezolizumab 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 5 months after the last dose of talimogene laherparepvec or atezolizumab.

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

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

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

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

In addition to reporting a lactation case during the study, investigators should monitor for lactation cases that occur through 5 months after the last dose of talimogene laherparepvec or atezolizumab.

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

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

9.4 Reporting of Exposure to Talimogene Laherparepvec

If a household member, caregiver, or healthcare provider who has had close contact with a subject treated with talimogene laherparepvec on this study is suspected to have been exposed to talimogene laherparepvec (eg, have or who have had signs or symptoms suspected to be herpetic in origin or who have been 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 knowledge of the event of exposure. Amgen will seek to follow-up with the exposed individual, if necessary, to collect more information about the exposed individual contact with clinical trial subject, signs and/or symptoms related to the exposure, medical history, and/or outcome of the exposure. If the exposed individual is reporting sign or symptoms suspected to be related to talimogene laherparepvec exposure, the exposed individual may be asked to have a swab taken to evaluate for the presence of talimogene laherparepvec DNA in the lesion.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

10.1.1.1 Primary Endpoints

- Subject incidence of DLTs by tumor type (triple negative breast cancer and colorectal cancer)

10.1.1.2 Secondary Endpoints

- ORR, BOR, DOR, lesion level responses (≥ 30% and 100% decrease) in injected and uninjected lesions (overall, hepatic, nonhepatic), DRR, DCR, PFS, and OS by tumor type (triple negative breast cancer and colorectal cancer)

10.1.1.3 Safety Endpoint

- Subject incidence of adverse events and clinically relevant laboratory abnormalities by tumor type (triple negative breast cancer and colorectal cancer)

10.1.1.4 Exploratory Endpoints

- Changes in tumor inflammation markers such as PD-L1 analysis and CD8 density
- Identification of potential blood and tumor biomarkers which correlate with or predict clinical outcomes

10.1.2 Analysis Sets

10.1.2.1 DLT Analysis Set

The DLT analysis set will include DLT-evaluable subjects who have had the opportunity to be on treatment for at least 6 weeks from the initial dose of study treatment and have received at least 2 doses of talimogene laherparepvec and 2 doses of atezolizumab in combination, or have a DLT during the DLT evaluation period as described in Section 3.1.

10.1.2.2 Safety Analysis Set

The safety analysis set will include all subjects who received at least 1 dose of talimogene laherparepvec or atezolizumab.

10.1.2.3 Biomarker Analysis Sets

Biomarker analysis sets will be defined separately for each individual candidate biomarker. For predictive analyses, the analysis set will include all subjects in the safety analysis set with a baseline biomarker result and, for analyses of biomarker changes, the analysis set will include all subjects in the safety analysis set that have baseline and at least one subsequent biomarker result.

10.1.3 Covariates and Subgroups

For each tumor type the following covariates **may** be used to examine efficacy and safety in subgroups or in multivariate analyses as appropriate:

- Region, if applicable (USA vs non-USA)
- Age at baseline: < 50, ≥ 50; < 65, ≥ 65; < 75, ≥ 75 years
- Sex (female vs male)
- Prior lines of cancer therapy in metastatic setting (0, 1, 2, >2)
- HSV-1 serostatus (positive versus negative)
- Baseline lactate dehydrogenase (LDH) ≤ ULN vs > ULN
- ECOG performance status (0 versus 1)
- Brain metastases for triple negative breast cancer (yes or no),
- Baseline overall tumor burden
- Baseline liver tumor burden
- Prior exposure to chemotherapy (yes or no)
- Extrahepatic visceral metastases at baseline (yes or no)
- PD-L1 status (positive versus negative)
- MSI phenotype (yes, no, or unknown) (colorectal cancer cohort only)

- Receipt of non-hepatic talimogene laherparepvec (yes or no)
- Other covariates reported in the literature or from other Amgen/Genentech studies may be considered as appropriate at the time of analysis

10.2 Sample Size Considerations

The null hypothesis (H0) is that the combination of talimogene laherparepvec and atezolizumab has a DLT rate ≤ 10%. An unacceptable alternative hypothesis (Ha) is a true DLT rate ≥ 33%. The sample size goal is to have ≥ 80% power for a 1-sided ≤ 10% significance level test to reject H0 when Ha is true 1. Eighteen DLT-evaluable subjects in each cohort will be required to test H0. Assuming the incidence of DLTs is evaluated as specified by Table 3-1 in Section 3.1, this design achieves a 7.7% 1-sided significance level and 81.6% power.

10.3 Planned Analyses

10.3.1 Interim Analyses

No formal interim efficacy analysis is planned for this study. Interim safety analyses will be performed to support the evaluation of safety by the DLRT. Enrollment will be suspended at the first safety interim analysis when the first 4 to 6 DLT-evaluable subjects have been enrolled in the study. At the discretion of the DLRT, additional safety analyses may be conducted as warranted. If the DLRT does not prematurely end enrollment, the safety of the combination will be evaluated on the first 18 DLT-evaluable subjects in each cohort.

10.3.2 Dose Level Review Team

DLRT meetings will be held to review data, monitor safety, and make dose decisions. The review team will be composed of the investigator(s), Amgen Medical Monitor, Genentech representative, Amgen Global Safety Officer or designated safety scientist, Amgen Global Clinical Trial Manager, and Amgen Biostatistics representative. Additional members may be added as needed (eg, Global Development Leader). A quorum, defined as > 50% of the participating investigators who have enrolled subjects in the study or their qualified designee [ie, sub-PI or research nurse or study coordinator possessing hard copy documentation (eg, email) of the PI's vote regarding the dose level review], must be in attendance for each DLRT meeting. The DLRT will be rescheduled if a quorum is not reached. The DLRT members are responsible for dosing decisions, which may include continuation, delay, or termination of dosing. All available study data, including demographics, investigational product administration, medical history, concomitant medications, adverse events, ECGs, vital signs, laboratory results

will be reviewed. In addition to DLTs, all ≥ grade 3 treatment emergent toxicities not meeting DLT criteria will be reviewed by the team and can be considered in the DLRT's decisions. Data to be reviewed will be queried.

10.3.3 Primary Analysis

The primary analyses will be performed separately for each cohort if the expected data cutoff dates for the two cohorts exceed 3 months. The primary safety analyses will occur when the last DLT-evaluable subject in the cohort is enrolled and has had the opportunity to complete the DLT evaluation period.

The primary efficacy analyses will occur 19 weeks after the last DLT-evaluable subject in the cohort is enrolled.

10.3.4 Final Analysis

The final analyses will be performed separately for each cohort and will occur when the last subject in the cohort has discontinued study treatment and has had the opportunity to complete the long-term survival follow-up visit. The final analyses will be performed separately for each cohort if the expected data cutoff dates for the two cohorts exceeds 3 months.

10.4 Planned Methods of Analysis

10.4.1 General Considerations

The data will be analyzed by cohort. Besides a summary of the incidence of DLTs, descriptive statistics will be provided for demographic, safety, efficacy, and biomarkers as appropriate.

10.4.2 Primary Endpoint

The DLT analysis set will be used to summarize the subject incidence of DLTs for the study and the safety analysis set will be used for all other analyses of safety endpoints. The efficacy analysis will be conducted using the safety analysis set unless otherwise specified.

10.4.3 Efficacy Endpoints

ORR, BOR, DRR, DCR will be summarized with the associated 95% CI. The proportion of all evaluable injected and uninjected lesions with a response (≥ 30% and 100% decrease) will be summarized by lesion type (overall, hepatic, non-hepatic). DOR, PFS and OS will be summarized and estimated using the Kaplan-Meier method.

10.4.4 Safety Endpoints

Subject incidence of treatment-emergent and treatment-related adverse events (including all 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. Treatment-emergent adverse events are defined as adverse events with an onset from the first dose of study therapy up to 30 days after the last dose of study therapy.

Subject incidence of disease-related events and fatal disease-related events will be tabulated by system organ class and preferred term. A sensitivity analysis of treatment-emergent adverse events will be conducted that considers any disease-related event as an adverse event if the disease-related event was reported in the study for any subject as a treatment-emergent adverse event.

Medical Dictionary for Regulatory Activities (MedDRA) will be used to code adverse events to a system organ class and a preferred term within the system organ class. The CTCAE version 4.0 will be used to grade severity of adverse events. Subject incidence of disease related events and fatal disease related events will be tabulated by system organ class and preferred term.

Summary statistics will be provided for vital signs, physical measurements and laboratory data.

Full details of the analysis will be provided in the statistical analysis plan.

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

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

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject or legally acceptable representative 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(s) is/are administered. A legally acceptable representative is an

individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study.

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 informed consent form is to be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the subject or a legally acceptable representative.

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 informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood.

11.2 Institutional Review Board/Independent Ethics Committee

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

The investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent document. The investigator is to notify the IRB/IEC of deviations from the protocol or serious adverse events occurring at the site and other 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 informed consent forms) are to be kept in confidence by the investigator, except as described below.

In compliance with governmental regulations and International Council for Harmonisation (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

Amgen may amend the protocol at any time. After Amgen amends the protocol, the Investigator is to return the signed Investigator's Signature page confirming agreement to continue participation in the study according to the amendment. 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 and amended protocol Investigator's Signature page to Amgen prior to implementation of the protocol amendment at their site.

Amgen reserves the right to terminate the study at any time. Both Amgen and the Investigator reserve the right to terminate the Investigator's participation in the study according to theClinical Trial Agreement. 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 IxRS system captures the following data points and these are considered source data: subject identification number.

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

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for

inspection at any time by representatives from Amgen and/or applicable regulatory authorities.

Elements to include:

- Subject files containing completed CRFs, informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the IRB/IEC and Amgen
- Investigational product-related correspondence including Proof of Receipts (POR), Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable.
- Non-investigational product(s) and or medical device(s) documentation, 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 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 R&D Compliance and Audit (or designees). Inspection of site facilities (eg, pharmacy, protocol-required therapy storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Data capture for this study is planned to be electronic:

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

12.4 Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including subjects not receiving protocol-required therapies) as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Assessments (**Table 7-1**), the investigator can search publicly available records [where permitted]) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

12.5 Language

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood. CRFs must be completed in English. Trade names® (if used) for concomitant medications may be entered in the local language.

12.6 Publication Policy

To coordinate dissemination of data from this study, Amgen may facilitate the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other investigators and to collaborate with authors and Amgen staff as appropriate as defined in the Publication Charter. Membership on the committee (both for investigators and Amgen staff) does

not guarantee authorship. The criteria described below are to be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors [ICMJE])Recommendations for the Conduct of Reporting, Editing, and Publication 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; (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

Adams S, Gray R, Demaria S et al. Prognostic value of tumor-infiltrating lymphocytes in triple-negative breast cancers from two phase III randomized Adjuvant Breast Cancer trials: ECOG 2197 and ECOG 1199. *J Clin Oncol*. 2014: 32;2959-66

Amgen. Talimogene laherparepvec Investigator's Brochure.

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*. 2015a;31(suppl). Abstract LBA9008.

Andtbacka RH, Kaufman HL, Collichio F, et al. Talimogene Laherparepvec Improves Durable Response Rate in Patients With Advanced Melanoma. *J Clin Oncol.* 2015b;33(25):2780-2788.

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.

Alexandrov LB, Nik-Zainal S, Wedge DC, et al. Signatures of mutational processes in human cancer. *Nature* 2013;500:415–421.

Blank C, Gajewski TF, Mackensen A. Interaction of PD-L1 on tumor cells with PD-1 on tumor-specific T-cells as a mechanism of immune evasion: implications for tumor immunotherapy. *Cancer Immunol Immunother.* 2005;54:307–314.

Blank C, Mackensen A. Contribution of the PD-L1/PD-1 pathway to T-cell exhaustion: an update on implications for chronic infections and tumor evasion. *Cancer Immunol Immunother.* 2007;56:739–745.

Brahmer JR, Tykodi SS, Chow LQM, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Eng J Med.* 2012;366:2455-2465.

Center MM, Jemal A, Smith RA, Ward E. Worldwide variations in colorectal cancer. *Cancer J Clin*. 2009;59:366-378.

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).

Cody JJ, Hurst D. Promising oncolytic agents for metastatic breast cancer treatment. *Oncolytic Virother.* 2015;4:63-73.

Dent R, Trudeau M, Protchard KI, et al. Triple-Negative Breast Cancer: Clinical Features and Patterns of Recurrence. *Clin Cancer Res.* 2007;13:4429-4434.

Dieci MV, Criscitiello C, Goubar A et al. Prognositic value of tumor-infiltrating lymphocytes on residual disease after primary chemotherapy for triple-negative breast cancer: a retrospective multicenter study. *Annals of Oncology*. 2014;25:611-618.

Emens L, Braiteh F, Cassier P, et al. Inhibition of PD-L1 by MPDL3280A leads to clinical activity in patients with metastatic triple-negative breast cancer (TNBC). *Cancer Res* 2015;75(15 Suppl):Abstract nr 2859.

Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicenter, open-label, phase 2 randomised controlled trial. *The Lancet*. 2016; 387:1837-1846.

FDA Guidance for Industry - Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009 www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatory Information/Guidances/UCM174090.pdf

Foulkes WD, Smith IE, Reis-Filho JS. Triple-negative breast cancer. *N Engl J Med.* 2010;363(20):1938-1948.

Garon EB, Rizvi AN, Hui R et al. Pemborlizumab for the Treatment of Non-Small Cell *Lung Cancer*. 2014;372:2018-2028.

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.

Genenetech. Atezolizumab Investigator's Brochure.

Goldman AI. Issues in designing sequential stopping rules for monitoring side effects in clinical trials. *Control Clin Trials*. 1987;8:327-337.

Hamanishi J, Mandai M, Iwasaki M, et al. Programmed cell death 1 ligand 1 and tumor-infiltrating CD8 + T lymphocytes are prognostic factors of human ovarian cancer. *Proc Natl Acad Sci* USA 2007;104:3360–3365.

Haffty BG, Yang Q, Reiss M, et al. Locoregional relapse and Distant Metastasis in Conservatively Managed Triple Negative Early-Stage Breast Cancer. *J. Clin Oncol.* 2006;24:5652-5657.

Hecht J, Pless M, Cubillo A, et al. Early safety from a phase 1, multicenter, open-label clinical trial of talimogene laherparepvec (T-VEC) injected into liver tumors. Poster presented at: 2018 Gastrointestinal Cancers Symposium; 19 January 2018; San Francisco, CA.

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;19:329-336.

Hino R, Kabashima K, Kato Y, et al. Tumor cell expression of programmed cell death-1 ligand 1 is a prognostic factor for malignant melanoma. *Cancer.* 2010;116:1757–1766.

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

Hu JC, Coffin RS, Davis CJ, et al. A phase 1 study of OncoVEXGM-CSF, a second-generation oncolytic herpes simplex virus expressing granulocyte macrophage colony-stimulating factor. *Clin Cancer Res.* 2006;12:6737-6747.

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

Keir ME, Butte MJ, Freeman GJ, et al. PD-1 and its ligands in tolerance and immunity. *Annual Rev Immunol*. 2008;26:677–704.

Kilinc MO, Gu T, Harden JL, et al. Central role of tumor-associated CD8+ T effector/memory cells in restoring systemic antitumor immunity. *J Immunol.* 2009;182:4217–4225.

Kimata, Hm Tsuneo I, Kikumori T et al. Pilot Study of Oncolytic Viral Therapy Using Mutant Herpes Simplex Virus (HF10) against recurrent metastatic breast cancer. *Ann Surg Oncol*. 2006;13:1078-1084.

Kooby DA, Carew JF, Halternam MW et al. Oncolytic viral therapy for human colorectal cancer and liver metastases using a multi-mutated herpes simplex virus type-1 (G207). *FASEB J.* 1999;13:1325-1334.

Lawrence MS, Stojanov P, Polak P, et al. Mutational heterogeneity in cancer and the search for new cancer-associated genes. *Nature.* 2013;499:214–218.

Le DT, Ueam JN, Wang H, et al. PD-1 blockade in Tumors with Mismatch Repair Deficiency. *N Eng J Med*. 2015;372:2509-2520.

Lehmann BD, Bauer JA, Chen X, et al. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapy. *J Clin Invest.* 2011;121:2750-2767.

Lin NU, Claus E, Sohl J, Razzak AR, Arnaout A, Winer EP. Sites of distant recurrence and clinical outcomes in patients with metastatic triple-negative breast cancer: high incidence of central nervous system metastases. *Cancer.* 2008;113:2638-2645.

Lipson EJ, Sharfman WH, Charles DG, et al. Durable Cancer Regresison Off-treatment and Effective Re-induction Therapy with an Anti-PD-1 Antibody. *Clin Can Res*. 2013;19:462-468.

Llosa NH, Cruise M, Tam A et al. The Vigorous Immune Micorenvironment of Microsatellite Instable Colon Cancer is Balanced by Multiple Counter-Inhibitor check points. *Cancer Discov*. 2015;5:43-51.

Lochhead P, Kuchiba A, Imamura Y et al. Microsatellite instability and BRAF mutation testing in colorectal cancer prognostication. *J Natl Cancer Inst.* 2013;105:1151-1156.

Long GV, Reinhard D, Ribas A, et al. Primary analysis of MASTERKEY-265 phase 1b study of talimogene laherparepvec (T-VEC) and pembrolizumab (pembro) for unresectable stage IIIB-IV melanoma. (abstract) 2015; Society for Melanoma Research 2015 Congress. http://www.melanomacongress.com/docs/SMR_2015_Congress_Late_Breaking_Abstracts.pdf

Manfredi S, Lepage C, Hatem C, Coatmeur O, FaIVRSe J, Bouvier AM. Epidemiology and management of liver metastases from colorectal cancer. *Ann Surg*. 2006 Aug;244(2):254-259.

Mu CY, Huang JA, Chen Y, et al. High expression of PD-L1 in lung cancer may contribute to poor prognosis and tumor cells immune escape through suppressing tumor infiltrating dendritic cells maturation. *Med Oncol.* 2011;28:682–688.

Nanda R, Chow LQ, Dees EC, et al.. A phase Ib study of pembrolizumab (MK-3475) in patients with advanced triple-negative breast cancer. San Antonio Breast Cancer Symposium: San Antonio, TX, 2014, December 8-13, 2014.

Nishino M, Gargano, M, Suda M, et al. 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.

Ono M, Tsuda H, Shimizu C, et al. Tumor-infiltrating lymphocytes are correlated with response to neoadjuvant chemotherapy in triple-negative breast cancer. *Breast Cancer Res Treat.* 2012;132:793-805.

Pages F, Berger F, Camus M, et al. Effector memory T-cells, early metastasis, and survival in colorectal cancer. *N Engl J Med.* 2005;353:2654–2666.

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; 9:533-542.

Puzanov I, Milhem MM, Andtbacka RHI, et al: Primary analysis of a phase 1b multicenter trial to evaluate safety and efficacy of talimogene laherparepvec (T-VEC) and ipilimumab (ipi) in previously untreated, unresected stage IIIB-IV melanoma. *J Clin Oncol 32*:578s, 2014 (suppl 15s; abstr 9029).

Rakha EA, Chan S. Metastatic Triple-negative Breast Cancer. *Clin Oncol*. 2011;23:587-600.

Rosenberg JE, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicenter, phase 2 trial. *The Lancet*. 2016;387:1909-1920.

Russell SJ ,Peng K, Bell JC. Oncolytic Virotherapy. *Nat Biotechnol*. 2014;30:1-29.

Sahin TT, Kasuya H, Nomura T, et al. Impact of novel oncolytic virus HF10 on cellular components of the tumor microenvironment in patients with recurrent breast cancer. *Cancer Gene Thera.* 2012;19:229-237.

Segal NH, Parsons DW, Peggs KS, et al. Epitope landscape in breast and colorectal cancer. *Cancer Res.* 2008;68:889–892.

Smyrk TC, Watson P, Kaul K, et al. Tumor-infiltrating lymphocytes are a marker for microsatellite instability in colorectal carcinoma. *Cancer.* 2001;91:2417-2422.

The Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute. SEER Stat Fact Sheets: Colon and Rectum Cancer. Available at seer.cancer.gov/statfacts/html/colorect.html

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

Thompson RH, Kuntz SM, Leibovich BC, et al. Tumor B7-H1 is associated with poor prognosis in renal cell carcinoma patients with long-term follow-up. *Cancer Res.* 2006;66:3381–3385.

Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti–PD-1 antibody in cancer. *N Engl J Med*. 2012;366:2443–2454.

Van Rooij N, van Buuren MM, Philips D, et al. Tumor Exome Analysis Reveals Neoantigen-Specific T-Cell Reactivity in an Ipilimumab-Responsive Melanoma. *J Clin Oncol.* 2013;31:1-8.

Youlden DR, Cramb SM, Dunn NA, Muller JM, Pyke CM, Baade PD. The descriptive epidemiology of female breast cancer: an international comparison of screening, incidence, survival and mortality. *Cancer Epidemiol*. 2012;36:237-248.

14. APPENDICES

Appendix A. Additional Safety Assessment Information

Adverse Event Grading Scale

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

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

Drug-induced Liver Injury Reporting & Additional Assessments Reporting

To facilitate appropriate monitoring for signals of Drug Induced Liver Injury (DILI), cases of concurrent aspartate aminotransferase (AST) or alanine aminotransferase (ALT), alkaline phosphatase (ALP), and total bilirubin 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 case report form (CRF) (eg, Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to the Amgen.

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 9.2.2.2.

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) is/are withheld (either permanently or conditionally) due to potential DILI as specified in Section 6.4.1 and Section 6.4.2 or who experience AST or ALT elevations > 3 x upper limit of normal (ULN) 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, alkaline phosphatase (ALP), bilirubin (total and direct), and INR within 24 hours
- In cases of total bilirubin > 2x 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 total bilirubin:
  - Obtain complete blood count with differential to assess for eosinophilia
  - Obtain serum total immunoglobulin 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 Hepatitis A, B, C viral serologies and human immunodeficiency virus (HIV)
  - Obtain creatinine phosphokinase (CPK), haptoglobin, lactate dehydrogenase (LDH), and peripheral blood smear
  - Perform appropriate liver imaging if clinically indicated
- Obtain hepatology consult (liver biopsy may be considered in consultation with an hepatologist)
- Follow the subject and the laboratory tests (ALT, AST, ALP, total bilirubin, 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 all investigational product(s) and protocol-required therapies.

The potential DILI event and additional information such as medical history, concomitant medications and laboratory results must be captured in corresponding CRFs.

Appendix B. Sample Serious Adverse Event Report Form

AMGEN Study # 20140299 Talimogene -Laherparepvec	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

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

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

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

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

3. SERIOUS ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day Month Year

Serious Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report *List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of IP	Is event serious?	If serious, enter Serious Criteria code (see codes below)	Relationship Is there a reasonable possibility that the Event may have been caused by IP or an Amgen device used to administer the IP? Talimogene Laherparepvec: No / Yes Aezolizumab: No / Yes <Blinded>: No / Yes <Blinded>: 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	☒ open label							Lot #_____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
Atezolizumab	☒ open label							Lot #_____ ☐ Unknown Serial # _____ ☐ Unavailable /

AMGEN
Study # 20140299
Talimogene -Laherparepvec

Electronic Serious Adverse Event Contingency Report Form

For Restricted Use

								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

AMGEN Study # 20140299 Talimogene -Laherparepvec	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

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

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

Appendix C. Pregnancy and Lactation Notification Worksheets

AMGEN Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: 20140299

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

2. Contact Information

Investigator Name _____ Site # _____

Phone (____)_____ Fax (____)_____ Email _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ Subject Gender: ☐ Female ☐ Male Subject DOB: mm / dd / yyyy_____

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
Talimogene Laherparepvec				mm /dd /yyyy_____

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

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

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

5. Pregnancy Information

Pregnant female's LMP mm / dd / yyyy_____ ☐ Unknown

Estimated date of delivery mm_____ / dd_____/ yyyy ___ ☐ Unknown ☐ N/A

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

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

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

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

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

_____

_____

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

Effective Date: March 27, 2011 Page 1 of 1

AMGEN Lactation Notification Worksheet

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

1. Case Administrative Information

Protocol/Study Number: 20140299

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

2. Contact Information

Investigator Name _____ Site # _____

Phone (____)_____ Fax (____)_____ Email _____

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

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

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

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

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

5. Breast Feeding Information

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

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

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

_____

_____

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

Effective Date: 03 April 2012, version 2. Page 1 of 1

Appendix D. Modified irRC-RECIST Guidelines for Assessment of Disease Response

The Immune-related Response Criteria (irRC) simulating Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1(irRC-RECIST) defined by Nishino et al, 2014, with modification will be 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 of Tumor Lesions

Computed Tomography Scans (or Magnetic Resonance Imaging):

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 contrast for CT scans while on trial. This change would require the preapproval of the Amgen medical monitor.

Positron Emission Tomography (PET)/CT Scans:

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

Ultrasound:

Ultrasound should not be used as a primary method to assess lesion measurements in response to treatment. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is needed.

Clinical Lesion Measurements

Clinical lesions will only be considered measurable when they are superficial and ≥10 mm in diameter as assessed using calipers (eg, skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken.

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

Measurability of Tumor Lesions at Baseline

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
- ≥ 10 mm caliper measurement by clinical exam for superficial cutaneous or subcutaneous lesion as measured by caliper
- 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 total (maximum 5 per organ) at baseline and new measurable lesions 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 be removed via interventional procedures, which can lead to a false interpretation of disease response. These fluid collections should not be used as baseline non-target lesions or as evidence of disease response.

Bone Lesions

- Bone scans, PET scans or plain films are not considered adequate imaging techniques to measure 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 as 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 localized therapies (eg, radiation, ablation, embolization), 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 of diameters.

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 the study. 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'.

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 (for which the longest diameter is ≥ 10 mm for non-nodal lesions or the short axis is ≥ 15 mm for nodal lesions) are added together to provide the total tumor burden. If more than 10 new measurable lesions total (or 5 per organ) are present, 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 the new measurable lesion limit during the course of the study for one subject, the additional lesions would be considered new non-measurable lesions.

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

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

For non-nodal target lesions that become 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 an actual measurement is able to be provided, this should be recorded even if it is <5 mm. If it is in the opinion of the radiologist that the non-nodal lesion has likely disappeared, the measurement should be recorded as “0 mm”. Nodal disease should always have the actual short axis measurement recorded even if the nodes regress to below 10 mm on study.

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 complete response (CR), the presence of any non-target and/or new non-measurable lesions. The overall response is derived from timepoint response assessments as described in Table 14-1 and Table 14-2.

Table 14-1. 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 from the date first documented. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm. If tumor markers are initially above the upper limit of normal, they must normalize to be considered CR.
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.
Not Applicable (NA)	No target lesions were identified at baseline

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

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

Table 14-2. Matrix for Determining the Overall Response at Each Assessment Point

Measurable Response	Overall Response	
Target and new, measurable lesions (tumor burden)[a], %	Non-target (nonmeasurable and new nonmeasurable)	Using irRC-RECIST
↓100[b]	Absent/NA[c]	CR[d]
↓100	Present/ND	PR[d]
↓100	Unequivocal progression	PR[d]
↓≥ 30	Absent/Present NA[c]	PR[d]
↓≥ 30	Unequivocal progression	PR[d]
↓< 30 to ↑< 20	Absent/Present/NA/ND[c]	SD
↓< 30 to ↑< 20	Unequivocal progression	SD
↑≥ 20[e]	Any	PD[b, d]
UE	Any	UE
ND	Any	UE
NA[f]	Any	UE

CR = complete response; irRC-RECIST = immune-related response criteria Response Evaluation Criteria in Solid Tumors; NA = not applicable; ND = not done; PD = progressive disease; PR = partial response; SD = stable disease; UE = unevaluable

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

[b] 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.

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

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

[e] In addition to relative increase of ≥ 20%, the tumor burden must also demonstrate an absolute increase of ≥ 5 mm from nadir for PD.

[f] No target lesions identified at baseline. When a subject has only non-measurable disease (ie, no target lesions identified at baseline) the response will be unevaluable.

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

Subjects are considered to have PR or SD even if new lesions were present, as long as they met the respective thresholds of response as described in Table 14-2.

The best overall response for an unconfirmed CR or PR will be SD, and it will be UE if the last overall response is PD in the absence of consecutive confirmation or clinical deterioration. A best overall response of SD requires a visit response of SD or better no earlier than 63 days after the start of treatment; otherwise the overall response will be UE.

Confirmation of Response (CR or PR)

To be assigned a BOR of CR or PR, a corresponding overall visit response of CR or PR 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 post baseline tumor assessment, then confirmation of PD by a second assessment ≥ 4 weeks (28 days) later in the absence of rapid clinical deterioration (eg, 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 2 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).

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.

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

The procedure itself and all post-procedure lesion assessments should always be recorded in the CRF. A completely resected lesion should be assigned a default code of 0 mm (for target lesions) or “absent” (for non-target lesions). A partially resected lesion should be assigned its measurement post-procedure (for target lesions) or “present” (for non-target lesions). If the resected lesion contained no cancer 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 cancer 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.

For resected lymph nodes, refer to Table 14-3 below **for pre-procedure measurements**.

Table 14-3. 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 eCRF.

[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.

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 considered measurable. Any new lesions that result from separating should be documented as lesions that were generated by separating and not truly new lesions. When a non-target lesion splits into 2 or more lesions, the split parts remain non-target lesions for the duration of the study.

Appendix E. Eastern Cooperative Oncology Group (ECOG) Performance Status

Grade	ECOG Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self care; confined to a bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

Appendix F. Dose Medication Guidelines for Atezolizumab Related Adverse Events

Management of Atezolizumab-Specific Adverse Events

Toxicities associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, should be used to evaluate for a possible immunogenic etiology.

Although most immune-related AEs observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab may not have an immediate therapeutic effect, and in severe cases, immune-related toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

The investigator should consider the benefit-risk balance a given patient may be experiencing prior to further administration of atezolizumab. In patients who have met the criteria for permanent discontinuation, resumption of atezolizumab may be considered if the patient is deriving benefit and has fully recovered from the immune-related event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Pulmonary Events

Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab. Patients will be assessed for pulmonary signs and symptoms throughout the study and will also have CT scans of the chest performed at every tumor assessment.

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. Management guidelines for pulmonary events are provided in Table 14-4.

Table 14-4. Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
Pulmonary event, Grade 1	• Continue atezolizumab and monitor closely. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist.
Pulmonary event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Bronchoscopy or BAL is recommended. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

BAL = bronchoscopic alveolar lavage; IVIG = intravenous immunoglobulin

[a] Atezolizumab may be withheld for a longer period of time (ie, > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Hepatic Events

Immune-related hepatitis has been associated with the administration of atezolizumab. Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in Table 14-5.

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Patients with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have LFTs performed immediately and reviewed before administration of the next dose of study drug.

For patients with elevated LFTs, concurrent medication, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate.

Table 14-5. Management Guidelines for Hepatic Events

Event	Management
Hepatic event, Grade 1	• Continue atezolizumab. • Monitor LFTs until values resolve to within normal limits.
Hepatic event, Grade 2	All events: • Monitor LFTs more frequently until return to baseline values. Events of > 5 days' duration: • Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Hepatic event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

LFTs = liver function tests.

[a] Atezolizumab may be withheld for a longer period of time (ie, > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Gastrointestinal Events

Immune-related colitis has been associated with the administration of atezolizumab. Management guidelines for diarrhea or colitis are provided in Table 14-6.

All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. For events of significant duration or magnitude or associated with signs of systemic inflammation or acute-phase reactants (eg, increased CRP, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with 3 to 5 specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.

Table 14-6. Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

Event	Management
Diarrhea or colitis, Grade 1	• Continue atezolizumab. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for >7 days. • Monitor closely.
Diarrhea or colitis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate symptomatic treatment. • Patient referral to GI specialist is recommended. • For recurrent events or events that persist >5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Diarrhea or colitis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to gastrointestinal specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to gastrointestinal specialist for evaluation and confirmation biopsy. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

IV = intravenous

[a] Atezolizumab may be withheld for a longer period of time (ie, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Endocrine Events

Thyroid disorders, adrenal insufficiency, diabetes mellitus and pituitary disorders have been associated with the administration of atezolizumab. Management guidelines for endocrine events are provided in Table 14-7.

Patients with unexplained symptoms such as headache, fatigue, myalgias, impotence, constipation, or mental status changes should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. The patient should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free T3 and T4 levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (eg, TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone [ACTH] levels and ACTH stimulation test) and magnetic resonance imaging (MRI) of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Table 14-7. Management Guidelines for Endocrine Events

Event	Management
Asymptomatic hypothyroidism	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly.
Symptomatic hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving.
Asymptomatic hyperthyroidism	TSH ≥ 0.1 mU/L and < 0.5 mU/L: • Continue atezolizumab. • Monitor TSH every 4 weeks. TSH < 0.1 mU/L: • Follow guidelines for symptomatic hyperthyroidism.
Symptomatic hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab and contact Medical Monitor for life-threatening immune-related hyperthyroidism.[c]

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Footnotes defined on last page of table

Table 14-7. Management Guidelines for Endocrine Events

Event	Management
Symptomatic adrenal insufficiency, Grade 2–4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Hyperglycemia Grade 1 or 2	• Continue atezolizumab. • Initiate treatment with insulin if needed. • Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with insulin. • Monitor for glucose control. • Resume atezolizumab when symptoms resolve and glucose levels are stable.
Hypophysitis pan-hypopituitarism), Grade 2-3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.[a] • Initiate hormone replacement therapy if clinically indicated. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent hypophysitis, treat as a Grade 4 event.

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Footnotes defined on last page of table

Table 14-7. Management Guidelines for Endocrine Events

Event	Management
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor.[c] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.[a] • Initiate hormone replacement therapy if clinically indicated.

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MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone, IV = intravenous

[a] Atezolizumab may be withheld for a longer period of time (ie, > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Ocular Events

An ophthalmologist should evaluate visual complaints (eg, uveitis, retinal events).

Management guidelines for ocular events are provided in Table 14-8.

Table 14-8. Management Guidelines for Ocular Events

Event	Management
Ocular event, Grade 1	• Continue atezolizumab. • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If symptoms persist, treat as a Grade 2 event.
Ocular event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Ocular event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to ophthalmologist. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Atezolizumab may be withheld for a longer period of time (ie, > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.
[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.
[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Immune-Related Myocarditis

Immune-related myocarditis has been associated with the administration of atezolizumab. Immune-related myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Immune-related myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, eg, in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of pre-existing cardiac conditions, or progression of malignancy.

All patients with possible myocarditis should be urgently evaluated by performing cardiac enzyme assessment, an ECG, a chest X-ray, an echocardiogram, and a cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. An

endomyocardial biopsy may be considered to enable a definitive diagnosis and appropriate treatment, if clinically indicated.

Patients with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 14-9.

Table 14-9. Management Guidelines for Immune-Related Myocarditis

Event	Management
Immune-related myocarditis, Grade 1	• Refer patient to cardiologist • Initiate treatment as per institutional guidelines.
Immune-related myocarditis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to cardiologist • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Consider treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.[a] • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune-related myocarditis, Grade 3-4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to cardiologist • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. [a,b] • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

ECMO = extracorporeal membrane oxygenation; VAD = ventricular assist device; IV = intravenous.

[a] Atezolizumab may be withheld for a longer period of time (ie, > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Infusion Related Reactions

No premedication is indicated for the administration of cycle 1 of atezolizumab. However, patients who experience an infusion-related reaction with cycle 1 of atezolizumab may receive premedication with antihistamines or antipyretics/analgesics (eg, acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab associated infusion-related reactions, due to its potential for causing agranulocytosis.

Guidelines for medical management of infusion-related reactions during cycle 1 are provided in Table 14-10. For subsequent cycles, infusion-related reactions should be managed according to institutional guidelines.

Table 14-10. Management Guidelines for Infusion-Related Reactions

Event	Management
IRR, Grade 1	• Reduce infusion rate to half the rate being given at the time of event onset. • After the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. • If the infusion is tolerated at the reduced rate for 30 minutes after symptoms have resolved, the infusion rate may be increased to the original rate.
IRR, Grade 2	• Interrupt atezolizumab infusion. • Administer aggressive symptomatic treatment (eg, oral or IV antihistamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, oxygen). • After symptoms have resolved to baseline, resume infusion at half the rate being given at the time of event onset. ○ For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs.
IRR, Grade 3 or 4	• Stop infusion. • Administer aggressive symptomatic treatment (eg, oral or IV antihistamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, oxygen). • Permanently discontinue atezolizumab and contact Medical Monitor.[a]

IRR = infusion-related reaction; IV = intravenous.
[a] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Pancreatic Events

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate work-up should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table 14-11.

Table 14-11. Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Amylase and/or lipase elevation, Grade 2	• Continue atezolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (eg, >3 weeks), consider treatment with 10 mg/day oral prednisone or equivalent.
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to gastrointestinal specialist. • Monitor amylase and lipase every other day. • If no improvement, consider treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor. c
Immune-related pancreatitis, Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to gastrointestinal specialist. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor. [c]

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Footnotes defined on last page of table

Table 14-11. Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Immune-related pancreatitis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to gastrointestinal specialist. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

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IV = intravenous

[a] Atezolizumab may be withheld for a longer period of time (ie, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Dermatologic Events

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self limited, with or without pruritus. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table 14-12.

Table 14-12. Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	• Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (eg, antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab. • Consider patient referral to dermatologist. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve
Dermatologic event, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to dermatologist. • Initiate treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor.[c]

[a] Atezolizumab may be withheld for a longer period of time (ie, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Neurologic Disorders

Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table 14-13.

Table 14-13. Management Guidelines for Neurologic Disorders

Event	Management
Immune-related neuropathy, Grade 1	• Continue atezolizumab. • Investigate etiology.
Immune-related neuropathy, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Investigate etiology. • Initiate treatment as per institutional guidelines. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune-related neuropathy, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab and contact Medical Monitor.[c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of 1–2 mg/kg/day oral or IV prednisone or equivalent.

IV = intravenous

[a] Atezolizumab may be withheld for a longer period of time (ie, > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Immune-Related Meningoencephalitis

Immune-related meningoencephalitis is an identified risk associated with the administration of atezolizumab. Immune-related meningoencephalitis should be suspected in any patient presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness. Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process.

All patients being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or

edema. If deemed safe by the treating physician, a lumbar puncture should be performed and a neurologist should be consulted.

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 14-14.

Table 14-14. Management Guidelines for Immune-Related Meningoencephalitis

Event	Management
Immune-related meningoencephalitis, all grades	• Permanently discontinue atezolizumab and contact Medical Monitor. [a] • Refer patient to neurologist. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

IV = intravenous.
[a] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Immune-related Nephritis

Immune-related nephritis has been associated with the administration of atezolizumab. Eligible patients must have adequate renal function, and renal function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as non-steroidal anti-inflammatory drugs). Refer the patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment. If no alternative cause of acute kidney injury is identified, patients with signs and symptoms of acute kidney injury, in the absence of an identified alternate etiology, should be treated according to the management guidelines in Table 14-15.

Table 14-15. Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	• Continue atezolizumab. • Monitor kidney function, including creatinine, closely until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to renal specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab, and contact Medical Monitor. [c]
Renal event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. • Refer patient to renal specialist and consider renal biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute
Note: Management guidelines are presented by adverse event severity based on NCI CTCAE and are applicable to both CTCAE Version 4.0 and CTCAE Version 5.0.
[a] Atezolizumab may be withheld for a longer period of time (ie, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.
[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.
[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Immune-mediated Myositis

Immune-mediated myositis has been associated with the administration of atezolizumab. Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine kinase increase), and imaging (electromyography/magnetic resonance imaging [MRI]) features, and is confirmed with a muscle biopsy.

Patients with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 14-16.

Table 14-16. Management Guidelines for Immune-Mediated Myositis

Event	Management
Immune-mediated myositis, Grade 1	• Continue atezolizumab. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines.
Immune-mediated myositis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab, and contact Medical Monitor. [c]
Immune-mediated myositis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (eg, cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab, and contact Medical Monitor. [c] • For recurrent events, treat as a Grade 4 event.
Immune-mediated myositis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

Footnotes defined on next page

IV = intravenous

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Amendment 5

Protocol Title: A Phase 1b Study of Talimogene Laherparepvec in Combination With Atezolizumab in Subjects With Triple Negative Breast Cancer and Colorectal Cancer With Liver Metastases

Amgen Protocol Number (Talimogene Laherparepvec): 20140299

Amendment Date: 08 July 2019

Rationale:

This protocol is being amended to:

- Update to clarify the subjects enrolled in both cohorts 1 and 2 are “DLT-evaluable subjects”.
- Update to include results from randomized phase 3 trial (NCT02425891).
- Update approval status of atezolizumab in combination with nab paclitaxel.
- Update number of sites to delete the statement on closing sites that do not enroll within 6 months of site initiation.
- Delete disease related events section.
- Delete Self Evident Text
- Update immune-related response evaluation criteria in solid tumors (irRC-RECIST) to modified irRC-RECIST
- Update to include management guidelines for Immune-related nephritis and Immune-mediated myositis
- Make administrative and editorial changes

Description of Changes

Section: Global

Change: Typographical and editorial changes throughout.

Section: Global

Change: Changed date from 13 April 2018 to **08 July 2019**

Section: Title Page

Section: Title Page

Add:

Amendment 5	**08 July 2019**

Section: Synopsis, Study Design

Add:

This is a phase 1b, multicenter, open-label study to evaluate the safety of intrahepatic injection of talimogene laherparepvec in combination with intravenously administered atezolizumab in subjects with triple negative breast cancer and colorectal cancer with liver metastases. Talimogene laherparepvec will be injected intrahepatically in combination with intravenous atezolizumab to approximately 36 **DLT-evaluable** subjects in 2 parallel cohorts. Cohort 1 will comprise subjects with triple negative breast cancer with liver metastases (n =18 **DLT-evaluable subjects**). Cohort 2 will comprise subjects with colorectal cancer with unresectable liver metastases (n =18 **DLT-evaluable subjects**).

Section: Synopsis, Sample Size

Add:

Approximately 36 subjects will be enrolled (18 **DLT-evaluable** subjects in each cohort).

Section: Synopsis, Amgen Investigational Product Dosage and Administration and 6.2.1.1 Dosage, Administration, and Schedule, paragraph 2

Replace:

During the second cycle, talimogene laherparepvec will be administered up to 4.0 mL of 10^8 PFU/mL at week 4 of the study (+ 3 days).

With:

During the second cycle, talimogene laherparepvec will be administered up to 4.0 mL of 10^8 PFU/mL at week 4 of the study (± 3 days).

Section: Study Glossary

Add:

IV	**intravenous**
US	**United States**

Section: Study Design and Treatment Schema, footnote b

Add:

In the absence of confirmed PD per **modified** irRC-RECIST, atezolizumab treatment can continue after talimogene laherparepvec treatment has ended provided patient is tolerating atezolizumab and receiving clinical benefit in the opinion of the investigator.

Section: 2.1.2.1 Immunotherapy in Triple Negative Breast Cancer, paragraph 3

Replace:

After initial evidence of activity in triple negative breast cancer subjects in a phase 1/2 study, atezolizumab is now being further evaluated in combination with nab paclitaxel in a phase 3 trial (NCT02425891).

With:

After initial evidence of activity in triple negative breast cancer subjects in a phase 1/2 study, atezolizumab **was** evaluated in combination with nab-paclitaxel in a **randomized** phase 3 trial (NCT02425891) **of 902 patients with untreated metastatic triple negative breast cancer who were randomized 1:1 to atezolizumab plus nab-paclitaxel or placebo plus nab-paclitaxel. Median OS in the atezolizumab plus nab-paclitaxel arm was 21.3 months, and in the placebo plus nab-paclitaxel arm was 17.6 months (Hazard ratio for death, 0.84; P = 0.08); in patients with PD-L1 positive tumors, the median OS was 25.0 months for the atezolizumab plus nab-paclitaxel arm and 15.5 months for the placebo plus nab-paclitaxel arm (Hazard ratio 0.62). The rate of grade 3 or 4 adverse events was 48.7% in the atezolizumab plus nab-paclitaxel group and 42.2% in the placebo plus nab-paclitaxel group, with the most common being neutropenia, decreased neutrophil count, peripheral neuropathy, fatigue, and anemia. 57.3% in the atezolizumab plus nab-paclitaxel**

group and 41.8% in the placebo plus nab-paclitaxel group had an adverse event of special interest, suggestive of a potential immune-related etiology. Grade 3 or 4 adverse events of special interest occurred in 7.5% in the atezolizumab plus nab-paclitaxel group and 4.3% in the placebo plus nab-paclitaxel group. One grade 5 event of special interest (autoimmune hepatitis) occurred in the atezolizumab plus nab-paclitaxel group, and one grade 5 event of special interest (hepatic failure) occurred in the placebo plus nab-paclitaxel group. Adverse events that led to discontinuation of any agent occurred in 15.9% of subjects who received atezolizumab plus nab-paclitaxel, and in 8.2% of subjects who received placebo plus nab-paclitaxel. 6.4% discontinued atezolizumab because of adverse events, and 1.4% discontinued placebo because of adverse events. Based on the results of this trial, on March 8, 2019, the United States (US) Food and Drug Administration (FDA) granted accelerated approval for atezolizumab in combination with nab-paclitaxel for initial treatment of adult patients with unresectable locally advanced or metastatic triple negative breast cancer whose tumors express PD-L1, as determined by an FDA-approved test.

Section: 2.3 Non-Amgen Investigational Product Background: Atezolizumab, paragraph 3

Add:

Atezolizumab is approved in the United States and other countries for the treatment of urothelial carcinoma and is approved in the United States for the treatment of non-small cell lung cancer**. It is also approved in the United States in combination with nab-paclitaxel for the treatment of PD-L1 positive triple negative breast cancer** (refer to the prescribing information for specific indications).

Section: 3.1 Study Design

Replace:

This is a phase 1b, multicenter, open-label study to evaluate the safety of intrahepatic injection of talimogene laherparepvec in combination with intravenously administered atezolizumab in subjects with triple negative breast cancer and colorectal cancer with liver metastases. Approximately 36 subjects will be enrolled in two parallel cohorts. Cohort 1 will comprise triple negative breast cancer subjects with liver metastases (n = 18). Cohort 2 will comprise subjects with colorectal cancer with unresectable liver metastases (n = 18). Subjects will be treated with up to 4.0 mL of 10^6 PFU/mL

talimogene laherparepvec at cycle 1, day 1 followed by talimogene laherparepvec up to 4.0 mL of 10^8 PFU/mL 21+ 3 days later (cycle 2, day 1, week 4 of the study).

With:

This is a phase 1b, multicenter, open-label study to evaluate the safety of intrahepatic injection of talimogene laherparepvec in combination with intravenously administered atezolizumab in subjects with triple negative breast cancer and colorectal cancer with liver metastases. Approximately 36 **DLT-evaluable** subjects will be enrolled in two parallel cohorts. Cohort 1 will comprise triple negative breast cancer subjects with liver metastases (n = 18 **DLT-evaluable subjects**). Cohort 2 will comprise subjects with colorectal cancer with unresectable liver metastases (n = 18 **DLT-evaluable subjects**). Subjects will be treated with up to 4.0 mL of 10^6 PFU/mL talimogene laherparepvec at cycle 1, day 1 followed by talimogene laherparepvec up to 4.0 mL of 10^8 PFU/mL 21 **±** 3 days later (cycle 2, day 1, week 4 of the study).

Section: 3.2 Number of Sites

Delete:

~~Sites that do not enroll subjects within approximately 6 months of site initiation may be closed.~~

Section: 3.3 Number of Subjects, paragraph 2

Add:

Approximately 36 **DLT-evaluable** subjects will be enrolled (18 **DLT-evaluable** subjects in each cohort). Refer to Section 10.2 for sample size considerations.

Section: 4.1 Inclusion Criteria, criterion 104

Add:

104 Subjects with triple negative breast cancer with liver metastases, or subjects with colorectal cancer with liver metastases are eligible if they have had disease progression during or after ≥ 1 prior standard of care systemic anti-cancer therapy (eg, chemotherapy, targeted therapy) for metastatic disease **or if they progress during or within 6 months of receiving adjuvant therapy. If subjects, in the opinion of the investigator, are deemed not appropriate candidates for systemic anti-cancer therapy for metastatic disease or if they refuse systemic anti-cancer therapy for metastatic disease, they may be eligible after investigator discussion with sponsor medical monitor for approval.**

Section: 6.2.1.1 Dosage, Administration, and Schedule, Table 6-2, Talimogene Laherparepvec Injection Volume Guideline Based on Tumor Size for Cutaneous, Subcutaneous, and Nodal Lesions

Add:

Table 6-2. Talimogene Laherparepvec Injection Volume Guide**line** Based on Tumor Size for Cutaneous, Subcutaneous, and Nodal Lesions

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

Section: 6.2.1.1 Dosage, Administration, and Schedule, paragraph 16

Add:

The dose, start date, number of vials used per visit, **concentration,** and lot number of talimogene laherparepvec are to be recorded on each subject's CRF.

Section: 6.2.2.1 Dosage, Administration, and Schedule, paragraph 2

Add:

Atezolizumab is preferred to be given prior to talimogene laherparepvec.

Section: 6.2.2.1 Dosage, Administration, and Schedule, paragraph 3

Replace:

The first cycle of atezolizumab will be 21 (+ 3) days. Subsequent cycles of atezolizumab will be 21 (± 3) days. The dose level of atezolizumab is 1200 mg administered by intravenous infusion. In the absence of confirmed PD per irRC-RESIST, atezolizumab treatment can continue after talimogene laherparepvec treatment has ended provided patient is tolerating atezolizumab and receiving clinical benefit in the opinion of the investigator.

With:

The first cycle of atezolizumab will be 21 (+ 3) days. Subsequent cycles of atezolizumab will be 21 (± 3) days. The dose level of atezolizumab is 1200 mg administered by

intravenous infusion. In the absence of confirmed PD per **modified** irRC-RE**C**IST, atezolizumab treatment can continue after talimogene laherparepvec treatment has ended provided patient is tolerating atezolizumab and receiving clinical benefit in the opinion of the investigator.

Section: 6.5 Concomitant Therapy, paragraph 3

Add:

Systemic corticosteroids and TNF-α inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab but may be administered at the discretion of the treating physician after consultation with the Amgen medical monitor. If corticosteroids (prednisone > 10 mg or equivalent **daily**) or TNF-α inhibitors are needed for treatment of atezolizumab immune related adverse events, talimogene laherparepvec must be withheld until the corticosteroid dose is ≤ 10 mg prednisone or equivalent **daily** or TNF-. inhibitors are discontinued (see Section 6.2.1.3). If feasible, alternatives to corticosteroids should be considered.

Section: 6.6 Other Treatment Procedures, paragraph 2

Add:

If a subject demonstrates evidence of new or worsening CNS metastases, all study treatments should be withheld. After discussion between the Amgen medical monitor and the investigator to determine the appropriateness of treatment resumption provided CNS metastases are adequately treated, subjects may be allowed to remain on study. In addition, in order to resume talimogene laherparepvec or atezolizumab, corticosteroid dose must not exceed 10 mg of prednisone or equivalent **daily**. Re-exposure to talimogene laherparepvec and atezolizumab may occur only if the investigator and sponsor agree that the subject safety will not be compromised.

Section: 6.9 Excluded Treatments, Medical Devices, and/or Procedures During Study Period, bullet 3, sub-bullet 1

Add:

- If the subject requires corticosteroid dosing for related toxicities (eg, prednisone >10 mg or equivalent), talimogene laherparepvec dosing must be withheld until the corticosteroid dose is able to be decreased to ≤ prednisone 10 mg (or equivalent) **daily**.

Section: Table 7-1 Schedule of Assessments, footnote a

Add:

In the absence of confirmed PD per **modified** irRC-RECIST, atezolizumab treatment can continue after talimogene laherparepvec treatment has ended provided patient is tolerating atezolizumab and receiving clinical benefit in the opinion of the investigator.

Section: 9.1.1 Disease Related Events

Add:

Disease Related Events are events (serious or non-serious) anticipated to occur in the study population due to the underlying disease. **All serious disease related events will be recorded and reported to the sponsor or designee within 24 hours.** 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.

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.**

Section: 9.2.1 Reporting Procedures for Disease Related Events, paragraphs 1 and 3

Add:

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 atezolizumab through the safety follow-up visit (ie, 30 [+7] days after the last dose of talimogene laherparepvec or atezolizumab), are recorded on the Event CRF as a Disease-Related 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.

Section: 9.2.1 Reporting Procedures for Disease Related Events, paragraph 8

Add:

Disease-Related Events assessed by the investigator to be more severe than expected and/or related to the talimogene laherparepvec or atezolizumab, and determined to be serious, must be recorded on the Event CRF as Serious Adverse Events **and be recorded and reported per Section 9.1.1**.

Section: 12.3 Study Monitoring and Data Collection, paragraph 6

Delete:

~~Amgen (or designee) will perform Self-Evident Corrections (SEC) to obvious data errors in the clinical trial database. SECs will be documented in the CRF Standard Instructions and the CRF Specific Instructions, both of these will be available through the EDC system. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data (ie, same results sent twice with the same date with different visit, [eg, week 4 and early termination]) and updating a specific response if the confirming datum is provided in the "other, specify" field (eg, for race, reason for ending study).~~

Appendix A, Additional Safety Assessment Information, bullet 5

Delete:

- ~~Obtain appropriate blood sampling for pharmacokinetic analysis if this has not already been collected~~

Appendix D, Modified irRC-RECIST Guidelines for Assessment of Disease Response, Follow-up Assessment of Tumor Lesions, paragraph 1

Delete:

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 (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.

Appendix D, Modified irRC-RECIST Guidelines for Assessment of Disease Response, Response Evaluation, paragraph 11

Add:

For resected lymph nodes, refer to Table 14-3 below **for pre-procedure measurements**.

Section: Appendix F, Dose Medication Guidelines for Atezolizumab Related Adverse Events Management of Atezolizumab-Specific Adverse Events, Immune-related Nephritis and Immune-mediated Myositis

Add:

Immune-related Nephritis

Immune-related nephritis has been associated with the administration of atezolizumab. Eligible patients must have adequate renal function, and renal function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as non-steroidal anti-inflammatory drugs). Refer the patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment. If no alternative cause of acute kidney injury is identified, patients with signs and symptoms of acute kidney injury, in the absence of an identified alternate etiology, should be treated according to the management guidelines in Table 14-15.

Table 14-15. Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	• Continue atezolizumab. • Monitor kidney function, including creatinine, closely until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to renal specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab, and contact Medical Monitor. [c]
Renal event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. • Refer patient to renal specialist and consider renal biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute
Note: Management guidelines are presented by adverse event severity based on NCI CTCAE and are applicable to both CTCAE Version 4.0 and CTCAE Version 5.0.

[a] Atezolizumab may be withheld for a longer period of time (ie., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Immune-mediated Myositis

Immune-mediated myositis has been associated with the administration of atezolizumab. Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine kinase increase), and imaging (electromyography/magnetic resonance imaging [MRI]) features, and is confirmed with a muscle biopsy.

Patients with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 14-16.

Table 14-16. Management Guidelines for Immune-Mediated Myositis

Event	Management
Immune-mediated myositis, Grade 1	• Continue atezolizumab. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines.
Immune-mediated myositis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab, and contact Medical Monitor. [c]

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Footnotes defined on last page of table

Table 14-16. Management Guidelines for Immune Mediated Myositis (cont.)

Event	Management
Immune-mediated myositis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (eg, cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab, and contact Medical Monitor. [c] • For recurrent events, treat as a Grade 4 event.
Immune-mediated myositis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

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IV = intravenous

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Amendment 4

Protocol Title: A Phase 1b Study of Talimogene Laherparepvec in Combination With Atezolizumab in Subjects With Triple Negative Breast Cancer and Colorectal Cancer With Liver Metastases

Amgen Protocol Number 20140299

EudraCT number 2015-005480-16

NCT number NCT03256344

Amendment Date: 26 March 2018

Rationale:

This protocol is being amended to:

- Clarify the timing of the final analysis
- Clarify that atezolizumab treatment can continue after talimogene laherparepvec treatment has ended
- Update the end of study language and definitions
- Update rules for talimogene laherparepvec and atezolizumab withholding with regard to management of hepatic events
- Clarify that photographic equipment will not be provided by the sponsor, since photographs are not required for this study
- Clarify when a screening biopsy is required
- Add pharmacogenetics studies
- Make editorial, typographical, and formatting changes throughout the document

Amendment: Superseding Amendment 3

Protocol Title: A Phase 1b Study of Talimogene Laherparepvec in Combination With Atezolizumab in Subjects With Triple Negative Breast Cancer and Colorectal Cancer With Liver Metastases

Amgen Protocol Number Talimogene Laherparepvec (TVEC) 20140299

EudraCT number: 2015-005480-16

NCT number: 03256344

Amendment Date: 05 December 2017

Rationale:

This superseding amendment is being done to correct minor errors from the last amendment.

- Correct discrepancy between contraception language in the ICF and the protocol (polyurethane condom use allowed for those with latex allergies)
- Correct a discrepancy with radiographic imaging time points at safety follow-up between the Schedule of Assessments and footnotes (clarify that radiographic imaging is only needed at safety follow-up if a subject does not have confirmed disease progression and has not been scanned for 9 weeks).

Amendment 3

Protocol Title: A Phase 1b Study of Talimogene Laherparepvec in Combination With Atezolizumab in Subjects With Triple Negative Breast Cancer and Colorectal Cancer With Liver Metastases

Amgen Protocol Number 20140299

EudraCT number: 2015-005480-16

NCT number: 03256344

Amendment Date: 25 September 2017

Rationale:

The purpose of this protocol amendment is to:

- Update guidance on atezolizumab background and toxicity information to align with most recently approved language as provided by Genentech.
- Add guidance on the quantitative/qualitative reporting of resected lymph nodes.
- Update disease related event language.
- Address administrative, typographical, and formatting changes within the protocol.

Amendment 2

Protocol Title: A Phase 1b Study of Talimogene Laherparepvec in Combination With Atezolizumab in Subjects With Triple Negative Breast Cancer and Colorectal Cancer With Liver Metastases

Amgen Protocol Number (Talimogene laherparepvec) 20140299

EudraCT number 2015-005480-16

Amendment 2 Date: 21 February 2017

Rationale:

The intent of this amendment is to:

- Correct typographic errors in the inclusion criterion #109 (Section 4.1).
- Update footnotes in the Schedule of Assessments (Table 5).
- Clarify the timing of blood samples collection for tumor biomarkers (Section 7.3.13.1).
- Update the list of laboratory analytes (Table 6).
- Clarify the collection of liver tumor biopsies (Section 7.5.3).
- Update Table 8. Matrix for Determining the Overall Response at Each Assessment Point.
- Administration, typographical and formatting changes were made throughout the protocol.

Amendment 1

Protocol Title: A Phase 1b Study of Talimogene Laherparepvec in Combination With Atezolizumab in Subjects With Triple Negative Breast Cancer and Colorectal Cancer With Liver Metastases

Amgen Protocol Number 20140299

Amendment 1 Date: 04 November 2016

Rationale:

This protocol is being amended to:

- To update the required use of contraception for female patients to 5 months based on the latest update to the atezolizumab investigator brochure (IB)
- This IB update also required the prohibited use of live vaccine after treatment for atezolizumab to be extended to 5 months
- The language was updated to reflect the newest protocol template released:
  - The contraception language in the exclusion criteria was updated. This resulted in an additional language in Section 6 (Section 6.10 Contraceptive Requirements).
  - Table 6 Laboratory Analytes was updated
  - Section 9.2 Safety Event Reporting Procedures was updated
  - Section 9.3 Pregnancy and Lactation Reporting was updated
  - Section 12 Administrative and Legal Obligations was updated
- The exposure language for talimogene laherparepvec was updated to reflect the newest language as of 26 April 2016
- The End of Study language was updated for clarification
- Update language regarding diameter of tumors to clarify they will be assessed by ultrasound or computerized tomography (CT) in preparation for injection guidance.
- Clarify Grade $\geq$ 3 laboratory abnormality should be deemed to be not clinically significant by both the investigator and the sponsor.