Statistical Analysis Plan

Protocol Title:	Phase 2 Study of Talimogene Laherparepvec in Combination With Pembrolizumab in Subjects With Unresectable/Metastatic Stage IIIB-IVM1d Melanoma Who Have Progressed on Prior Anti-PD-1 Based Therapy
Short Protocol Title:	MASTERKEY-115
Protocol Number:	20180115
NCT Number:	NCT04068181
Authors:	[redacted]
Sponsor:	Amgen Inc. One Amgen Center Drive, Thousand Oaks, CA, 91320, USA
SAP Date:	**Document Version** — **Date** **Original (v1.0)** — 20 March 2020 **Amendment 1 (v2.0)** — 12 August 2021

Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	20MAR2020	
Amendment 1 (v2.0)	12AUG2021	[redacted] • **Updated** the date for this SAP amendment • **Updated** the List of Abbreviations • **Updated** the Introduction • **Updated** the Section 3.2 Sample size a total of **72** subjects were enrolled in the study (instead of N = 100 subjects planned at the beginning of the study). • **Updated** the Section 5. Definition Best overall response (iBOR) per modified irRC-RECIST **From:** … For the derivation of iBOR, the overall visit response will be considered iSD if it is an unconfirmed iCR or iPR, and iUE if it is either iSD earlier than **84** days after the date of first dose or an unconfirmed iPD when confirmation of iPD is required (ie, initial iPD without clinical instability). … **To:** … For the derivation of iBOR, the overall visit response will be considered iSD if it is an unconfirmed iCR or iPR, and iUE if it is either iSD earlier than **77** days after the date of first dose or an unconfirmed iPD when confirmation of iPD is required (ie, initial iPD without clinical instability). … And the corresponding Table 5-1. Matrix of Determining iBOR per Modified irRC-RECIST • **Updated** the Section 5. Definition Best overall response (iBOR) per modified irRC-RECIST • **Updated** the Section 5. Definition Best overall response (BOR) per modified RECIST 1.1 **From:**

		… For the derivation of BOR, the overall visit response will be considered UE if it is SD earlier than **84** days after the date of first dose. … **To:** … For the derivation of BOR, the overall visit response will be considered UE if it is SD earlier than **77** days after the date of first dose. … • **Updated** the Section 5. Definition Lesion-level **From:** Lesion-level endpoints will be censored **on or after** the earliest event of the start of the first subsequent anticancer therapy, merger with another lesion, or resection (except if pathology result indicates absence of melanoma). … **To:** Lesion-level endpoints will be censored **at** the earliest event of **after** the start of the first subsequent anticancer therapy, **on or after** merger with another lesion, or **on or after** resection (except if pathology result indicates absence of melanoma). … • **Updated** the Section 5. Definition PD-L1 Status **From:** PD-L1 expression from tumor biopsy tissue samples will be reported as positive or negative. PD-L1 expression is said to have positive status if the **tumor performance score (TPS)** is ≥ 1%, and negative status if **TPS** is <1%. **To:** PD-L1 expression is said to have positive status if the **combined positive score (CPS)** is ≥ 1%, and negative status if **CPS** is <1%. • **Updated** the Section 9.6.1 Adverse Events **From** "A listing of all AEs, EOIs for talimogene laherparepvec and pembrolizumab ECI will be provided. Listing of SAEs reported with event onset 90 days after the last dose of study therapy or 30 days after last

		dose of study therapy if the subject initiates new anticancer therapy, whichever is earlier, will be provided." **To:** "A Listing will be provided for treatment-emergent adverse events and treatment-emergent serious adverse events. In addition, death on study will be listed."

Table of Contents

List of Table

List of Appendices

List of Abbreviations

Abbreviation	Explanation
AE	Adverse Event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BOR	best overall response
BRAF^{V600}	serine/threonine protein kinase B-Raf V600
CI	confidence interval
CIF	Cumulative Incidence Function
CRF	case report form
CPS	**combined positive score**
CR	complete response (by modified RECIST 1.1)
CRR	complete response rate (by modified RECIST 1.1)
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate (by modified RECIST 1.1)
DOR	duration of response (by modified RECIST 1.1)
DRR	durable response rate (by modified RECIST 1.1)
DRT	data review team
ECG	electrocardiogram
ECI	events of clinical interest
ECOG PS	Eastern Cooperative Oncology Group Performance Status
FAS	Full Analysis Set
HSV	herpes simplex virus
iCR	complete response (by modified irRC-RECIST)
iCRR	complete response rate (by modified irRC-RECIST)
iDCR	disease control rate (by modified irRC-RECIST)
iDRR	durable response rate (by modified irRC-RECIST)
iDOR	duration of response (by modified irRC-RECIST)
iORR	objective response rate (by modified irRC-RECIST)
iPD	progressive disease (by modified irRC-RECIST)
iPR	partial response (by modified irRC-RECIST)
iPFS	progression free survival (by modified irRC-RECIST)
irRC-RECIST	immune-related Response Criteria simulating Response Evaluation Criteria in Solid Tumors
iSD	stable disease (by modified irRC-RECIST)
KM	Kaplan-Meier

LDH	lactate dehydrogenase
NCT	National Clinical Trials
ND	Not done
ORR	objective response rate (by modified RECIST 1.1)
OS	overall survival (by modified RECIST 1.1)
PD	Progressive disease (by modified RECIST 1.1)
PD-1	programmed cell death-1
PD-L1	programmed cell death-1 ligand 1
PFS	progression free survival (by modified RECIST 1.1)
PR	partial response (by modified RECIST 1.1)
qPCR	real-time polymerase chain reaction
RECIST	Response Evaluation Criteria in Solid Tumor
SAS	Safety Analysis Set
SD	Stable disease (by modified RECIST 1.1)
TEAE	Treatment Emergent Adverse Event
UE	Unevaluable
ULN	upper limit of normal
[redacted]	

1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol for study 20180115, Talimogene Laherparepvec (T-VEC), Amendment **3** dated **09 June 2021**. The scope of this plan includes the futility analysis, the primary analysis and the final analysis that are planned and will be executed by the Amgen Global Biostatistical Science department unless otherwise specified.

2. Objectives, Endpoints and Hypotheses

2.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of talimogene laherparepvec in combination with pembrolizumab as assessed by objective response rate (ORR) in subjects with unresectable/metastatic stage IIIB-IVM1d melanoma who have progressed on prior anti-PD-1 therapy	• Overall response (complete response [CR]+partial response [PR]) (by investigator assessment using modified RECIST v1.1)
Key Secondary	
• To evaluate the efficacy of talimogene laherparepvec in combination with pembrolizumab, as assessed by: ○ Complete response rate (CRR), best overall response (BOR), durable response rate (DRR), duration of response (DOR), and disease control rate (DCR) ○ ORR using modified irRC-RECIST ○ Progression free survival (PFS) ○ Overall survival (OS)	• Complete response, BOR, durable response, DOR and disease control, (investigator assessment using modified RECIST 1.1 and modified irRC-RECIST) and overall response using modified irRC-RECIST by investigator assessment • PFS (by investigator assessment using modified RECIST 1.1 and modified irRC-RECIST) • OS
• To evaluate the safety of talimogene laherparepvec in combination with pembrolizumab as assessed by incidence of treatment-emergent and treatment-related adverse events, and abnormal laboratory tests in patients who have progressed on prior anti-PD-1 therapy	• Incidence of treatment-emergent and treatment-related adverse events (all adverse events, grade ≥ 3 adverse events, serious adverse events, fatal adverse events, adverse events defined as events of interest), and abnormal laboratory tests

• To evaluate time to subsequent anticancer therapy	• Time to subsequent anticancer therapy

Exploratory	
[redacted]	

2.2 Hypotheses and/or Estimations

No formal hypothesis testing will be performed. All analyses will be descriptive in nature.

3. Study Overview

3.1 Study Design

This is a phase 2, open-label, single-arm, multicenter clinical trial designed to evaluate the efficacy and safety of talimogene laherparepvec in combination with pembrolizumab following disease progression on prior anti-PD-1 therapy in unresectable/metastatic melanoma (stage IIIB-IVM1d) or prior anti-PD-1 therapy in the adjuvant setting.

Subject must have received prior anti-PD-1 therapy for at least 2 to 3 consecutive cycles within an 8-week period (based on administration schedule) and have disease progression as defined by RECIST 1.1 criteria. The initial evidence of disease progression must have been confirmed by a second assessment no less than 4 weeks from the first documented disease progression, in the absence of rapid clinical progression. The anti-PD-1 therapy must be the immediate prior line of therapy before enrollment and subjects with disease progression on more than 1 line of anti-PD-1 therapy are not eligible.

Subjects will be enrolled into 1 of 4 cohorts based on prior anti-PD-1 experience:

- **Cohort 1 – Locally Recurrent/Metastatic - Primary Resistance**

  Subjects who received anti-PD1 therapy in the locally recurrent/metastatic setting and experienced a best overall response of disease progression or stable disease prior to confirmed disease progression. The initial date of disease progression must be within 12 weeks of the last dose of a PD-1 inhibitor.

- **Cohort 2 – Locally Recurrent/Metastatic - Acquired Resistance**

  Subjects who received anti-PD-1 therapy in the locally recurrent/metastatic setting and experienced confirmed disease progression following a complete or partial response on anti-PD-1 therapy. The disease progression must occur within 12 weeks of the last dose of a PD-1 inhibitor.

- **Cohort 3 – Adjuvant Setting – Disease Free Interval < 6 months**

  Subjects who received anti-PD-1 therapy in the adjuvant setting and experienced confirmed disease progression following a disease free interval of < 6 months after starting the adjuvant anti-PD-1 therapy.

- **Cohort 4 – Adjuvant Setting – Disease Free Interval ≥ 6 months**

Subjects who received anti PD-1 therapy in the adjuvant setting and experienced confirmed disease progression following a disease free interval of ≥ 6 months after starting the adjuvant PD-1 inhibitor.

3.2 Sample Size

This is a single-arm estimation study. It is assumed that if the ORR using modified RECIST v1.1 is at least 25%, for this study (N = 100) the lower bound of the 95% confidence interval for an objective response is > 15%.

The 95% CIs for different sample sizes with an assumed ORR of 25% are presented below:

Subjects Enrolled N	Assumed ORR N (%)	95% CI %	Width %
15	4 (26.7)	7.8, 55.1	47.3
30	8 (26.7)	12.3, 45.9	33.6
40	10 (25)	12.7, 41.2	28.5
70	18 (25.7)	16.0, 37.6	21.6
72	**18 (25.0)**	**15.5, 36.6**	**21.0**
100	25 (25)	16.9, 34.7	17.8

Actual number of subjects enrolled in the study: a total of 72 subjects were enrolled in the study (instead of N = 100 subjects planned at the beginning of the study). Twenty-seven subjects were enrolled into cohort 1 and 15 subjects were enrolled into cohorts 2, 3, and 4.

3.3 Adaptive Design

Futility analyses are planned for each of cohorts 1 and 2, separately. The futility criteria are detailed in Section 7.1.

4. Covariates and Subgroups

4.1 Planned Covariates

No covariate analyses will be performed.

4.2 Subgroups

Efficacy analyses on ORR and DCR will be repeated within the following subgroups, overall with cohorts pooled and separately for each cohort:

- Sex (female, male)
- Age at enrolment (<50, ≥50; < 65, ≥ 65; < 75, ≥ 75 years)
- Region (Europe, Non-Europe)
- PD-L1 status (positive, negative, missing/unknown) at baseline
- Disease stage (stage IVM1a or lower, stage IVM1b/c/d) at baseline
- Disease stage (stage IVM1b or lower, stage IVM1c/d) at baseline
- *BRAF*^{V600} mutation at baseline (yes, no)
- LDH (≤ ULN, > ULN; ≤ 2 x ULN, > 2 x ULN)
- ECOG PS (0, 1)
- HSV-1 serostatus at baseline (positive, negative, missing/unknown)
- In-transit disease at baseline (yes, no)
- Prior PD-1 therapy (nivolumab, ipilimumab/nivolumab, pembrolizumab, other)
- Prior anti-cancer therapy and line of therapy for current malignancy
- Prior surgery for current malignancy
- Prior radiotherapy for current malignancy

5. Definitions

- **Baseline**

Baseline in general refers to study day 1. The baseline value of a parameter (eg, vital signs, laboratory tests, and tumor measurement) is considered to be the latest value prior to receiving any study drug (i.e., on or prior to the first date of dosing). Parameters that are obtained on the same day as the first date of dosing are assuming to be pre-dose if the exact time of the baseline parameter relative to the first dose of any study drug is unknown. For subjects who are not dosed, the baseline value of a parameter is considered to be the latest value prior to the enrollment date. BRAF mutational status, which is not sensitive to treatment, will be considered baseline regardless of the timing of ascertainment.

- **Best overall response (iBOR) per modified irRC-RECIST**

iBOR of complete response (iCR), partial response (iPR), stable disease (iSD), progressive disease (iPD) or unevaluable (iUE) will be derived per modified irRC-RECIST based on investigator assessment. Overall visit response assessments occurring after the start of the first subsequent anticancer therapy will not be included. With the exception of a PD observation, overall visit response assessments occurring on or after a complete or

partial removal/reduction of any target lesion which contained melanoma on pathology evaluation or pathology results were unknown will not be included. The timepoint responses after initial confirmed iPD will not be used to derive BOR. Confirmation of iCR, iPR, and iPD is required as noted in the individual definitions for iCR, iPR and iPD per modified irRC-RECIST (refer to protocol Appendix 10). For the derivation of iBOR, the overall visit response will be considered iSD if it is an unconfirmed iCR or iPR, and iUE if it is either iSD earlier than **77** days after the date of first dose or an unconfirmed iPD when confirmation of iPD is required (ie, initial iPD without clinical instability). As indicated in Table 5.1, iBOR is defined as the best overall visit response in the following order: iCR, iPR, iSD, iPD, or iUE.

Table 5.1 Matrix of Determining iBOR per Modified irRC-RECIST

Visit Overall Response Sequence	Examples	Best Overall Response	Specifications
, iCR, iCR,	iPR, iCR, iCR iCR, iCR, iPD	iCR	A confirmatory iCR must be at least 4 weeks (28 days) later; a subsequent iCR within 28 days will not be valid for confirmation and will be ignored; the iCR will also not be confirmed if there is a subsequent iPR/iSD/iPD at any time prior to the next iCR.
:*, iPR, iPR, * *, iPR, iCR/iPR, non-iCR, *	iPR, iPR, iPD iPR, iCR, iPD iCR, iPR, iPD	iPR	Criteria for iBOR=iCR not met. A confirmatory iPR/iCR must be no less than 4 weeks (28 days) later; a subsequent iPR/iCR within 28 days will not be valid for confirmation and will be ignored; the iPR will also not be confirmed if there is a subsequent iSD/iPD at any time prior to the next iPR/iCR.
*, iSD, * *,iCR, non-iPR/iCR, * *,iPR, non-iPR/iCR, *	iCR iPD, iCR iPR iPD, iPR, iSD iSD iPD,iSD,iPD	iSD	Criteria for iBOR=iCR or iPR not met. iSD must be ≥ **77** days from date of first dose; however, this is not required for an unconfirmed iCR/iPR.

*,iPD, iPD, * *, iPDci, *	iPD, iPD iPD, iSD, iPD, iPD iPD, iUE, iPD iPDci	iPD	Criteria for iBOR= iCR, iPR, or iSD not met. A consecutive confirmatory iPD must be no less than 4 weeks (28 days) later unless the initial progression qualified for iPDci.; iPDci = the last available iPD "Nonconfirmed Disease Progression with Clinical Instability" as the reason for ending radiographic follow-up.
*, iSD, * iPD	iSD iUE, iSD iPD iUE, iPD	iUE	Criteria for iBOR=iCR, iPR, iSD, or iPD not met. iSD must be < **77** days from date of first dose.

- **Best overall response (BOR) per modified RECIST 1.1**

BORs will be derived based on investigator assessment using modified RECIST 1.1 (Eisenhauer *et al.* 2009). Per RECIST 1.1, a confirmation of CR or PR by a consecutive subsequent tumor assessment will not be required for the derivation of BOR. Overall visit response assessments occurring after the start of the first subsequent anticancer therapy will not be included. With the exception of a PD observation, overall visit response assessments occurring on or after a complete or partial removal/reduction of any target lesion which contained melanoma on pathology evaluation or pathology results were unknown will not be included. The timepoint responses after initial PD will not be used to derive BOR. For the derivation of BOR, the overall visit response will be considered UE if it is SD earlier than **77** days after the date of first dose. BOR is defined as the best overall visit response up to and including the first overall visit response of PD in the following order: CR, PR, SD, PD or UE.

- **Complete response rate (iCRR) per modified irRC-RECIST**

Complete response rate (iCRR) per modified irRC-RECIST is defined as the incidence of an iBOR of iCR per modified irRC-RECIST.

- **Complete response rate (CRR) per modified RECIST 1.1**

Complete response rate (CRR) per modified RECIST 1.1 is defined as the incidence of a BOR of CR per modified RECIST 1.1.

- **Disease control rate (iDCR) per modified irRC-RECIST**

Disease control rate (iDCR) per modified irRC-RECIST is defined as the incidence of an iBOR of iCR, iPR or iSD.

- **Disease control rate (DCR) per modified RECIST 1.1**

Disease control rate (DCR) per modified RECIST 1.1 is defined as the incidence of a BOR of CR, PR or SD.

- **Duration of response (iDOR) per modified irRC-RECIST**

Duration of response (iDOR) is defined as the time from the date of an initial response that is subsequently confirmed to the earlier of iPD (see definition of iBOR per modified irRC-RECIST) or death. Subjects who have not ended their response at the time of analysis will be censored at their last evaluable tumor assessment before the start of the first subsequent anticancer therapy.

- **Duration of response (DOR) per modified RECIST 1.1**

Duration of response (DOR) is defined as the time from the date of an initial response of CR or PR to the earlier of PD (see definition of BOR per modified RECIST 1.1) or death. Subjects who have not ended their response at the time of analysis will be censored at their last evaluable tumor assessment date before start of the first subsequent anticancer therapy.

- **Durable response rate (iDRR) per modified irRC-RECIST**

iDRR is defined as the percent of subjects with an iCR or iPR per modified irRC-RECIST with an iDOR ≥ 6 months. One month will be calculated based on 365.25 days per year.

- **Durable response rate (DRR) per modified RECIST 1.1**

DRR is defined as the percent of subjects with a CR or PR per modified RECIST 1.1 with a DOR ≥ 6 months. One month will be calculated based on 365.25 days per year.

- **End of study (trial) date**

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 (i.e., last subject last visit), following any additional parts in the study (e.g., long-term follow-up), as applicable.

- **Evaluable tumor assessment**

An overall visit response other than unevaluable (UE or iUE).

- **Events of clinical interest pembrolizumab**

Selected non-serious and serious adverse events known as pembrolizumab events of clinical interest (ECI) that occur after the first dose of pembrolizumab through 90 (+7) days after the last dose of pembrolizumab, or 30 (+7) days after initiation of a new anticancer therapy, whichever is earlier must be reported to Amgen within 24 hours.

- **Events of interest (EOI) for talimogene laherparepvec**

EOIs for talimogene laherparepvec are defined in the version-controlled EOI search strategies maintained by Global Regulatory Affairs and Safety (GRAAS) at Amgen for talimogene laherparepvec

- **Investigational product (IP)**

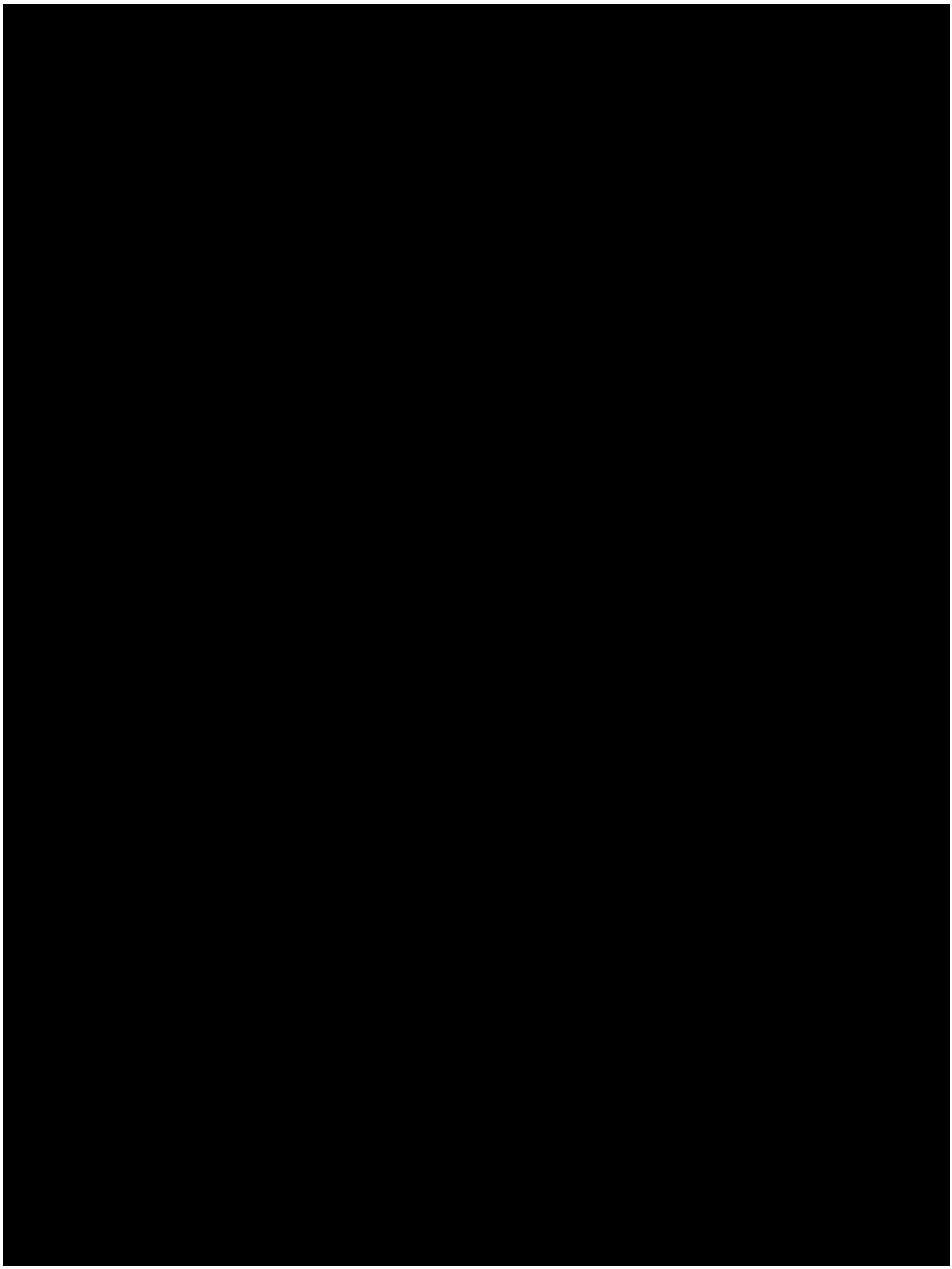
Investigational product (IP) refers to Amgen IP talimogene laherparepvec and non-Amgen IP pembrolizumab in this study. IP is also referred as study drug or study therapy.

- **Last date known to be alive**

For subjects not known to have died, their last date known to be alive will be determined as the latest date associated with clinic visits before data cutoff date including, for example, but not limited to the following:

1. Survival status: Last subject status date if status of subject is “Alive”
2. End of study date if the subject’s primary reason for ending study is not “Lost to follow-up”
3. Any subsequent anti-tumor therapy initialization date
4. AE start or end date
5. Procedure and concomitant medication start/end date
6. Date of lesion assessments
7. Date of herpetic lesion swabbing
8. Visit date of vital signs; physical exam; ECOG; sample collection for local lab and central lab parameters including HSV-1
9. Date of last investigational product administration

[redacted]



- **Objective response rate (ORR) per modified RECIST 1.1**

ORR is defined as the incidence of a BOR of CR or PR per modified RECIST 1.1. Subjects who do not have any post-baseline tumor assessments will be regarded as non-responders.

- **Objective response rate (iORR) per modified irRC-RECIST**

iORR is defined as the incidence of an iBOR of iCR or iPR per modified irRC-RECIST. Subjects who do not have any post-baseline tumor assessments will be regarded as non-responders.

- **Overall survival (OS)**

Overall survival is defined as the interval from first dose to death from any cause. Subjects without an event will be censored at the last date known to be alive.

- **PD-L1 Status**

PD-L1 expression from tumor biopsy tissue samples will be reported as positive or negative. PD-L1 expression is said to have positive status if the **combined positive score (CPS)** is ≥ 1%, and negative status if **CPS** is <1%.

- **Primary completion date**

The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoints 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 the last subject has completed the assessments for week 24.

- **Progression-free survival (iPFS) per modified irRC-RECIST**

iPFS per modified irRC-RECIST is defined as the interval from first dose to the earlier event of iPD (per modified irRC-RECIST) or death from any cause. Subjects without an event will be censored at their last evaluable post-baseline tumor assessment if available, otherwise will be censored on study day 1.

- **Progression-free survival (PFS) per modified RECIST 1.1**

PFS per modified RECIST 1.1 is defined as the interval from first dose to the earlier event of PD (per modified RECIST 1.1) or death from any cause. Subjects without an event will be censored at their last evaluable post-baseline tumor assessment if available, otherwise will be censored on study day 1.

- **Safety follow-up visit**

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

- **Serious adverse event (SAE)**

Serious adverse events (SAE) are defined as any adverse event categorized as serious as determined by investigator per protocol defined criteria.

- **Study day**

Study day is calculated from the first day IP is administered (i.e. non-zero dosing).

If visit date is on or after first dose date then:

Study day = visit date – first dose date + 1

if visit date is before first dose date then:

Study day = visit date – first dose date

- **Study week 0**

The start of IP administration (i.e. non-zero dosing) to the subject is study week 0. Study day 1 is corresponding to study week 0.

- **Time to subsequent anticancer therapy**

Time to subsequent anticancer therapy is defined as the time from enrollment to the start of subsequent anticancer therapy. Subjects who have not started subsequent anticancer therapy will be censored on their last visit date.

- **Treatment-emergent adverse events (TEAE)**

Treatment-emergent adverse events are defined as any adverse event occurring after initiation of the first dose of study therapy through 30 days after the last administration of study therapy. Adverse events that occur on the same day as the first dose date of study therapy will be treated as treatment-emergent events unless indicated otherwise (for example, if an event occurs on the same date as the first administration of study therapy and the check box indicating prior to the first dose of study therapy is checked on eCRF, then the event will not be counted as a treatment-emergent AE).

- **Treatment-emergent serious adverse events (TESAE)**

Treatment-emergent serious adverse events are defined as any SAE occurring after initiation of the first dose of study therapy through 90 days after the last administration of study therapy or 30 days after the last administration of study therapy if the subject initiates new anti-cancer therapy, whichever is earlier.

SAEs that occur on the same day as the first dose date of study therapy will be treated as treatment-emergent SAEs unless indicated otherwise (for example, if an event occurs on the same date as the first administration of study therapy and the check box indicating prior to the first dose of study therapy is checked on eCRF, then the event will not be counted as a treatment-emergent SAE).

- **Treatment period**

Treatment period is defined as the period between the first date of study therapy administration and 30 days after the last study therapy administration.

[redacted]

6. Analysis Set

6.1 Full Analysis Set

The Full Analysis Set (FAS) is defined as all enrolled subjects who have received at least 1 dose of talimogene laherparepvec and 1 dose of pembrolizumab in combination. The FAS will be used in the analysis of the efficacy endpoints.

6.2 Safety Analysis Set

The Safety Analysis Set (SAS), defined as all enrolled subjects who received at least 1 dose of talimogene laherparepvec or pembrolizumab, will be used in the analysis of the safety endpoints.

6.3 Per Protocol Set(s)

The Per Protocol Analysis Set (PPAS) is a subset of the FAS which includes subjects who do not have important protocol deviations that are considered to have an impact on efficacy outcomes.

Subjects with any of the following eligibility criteria for important protocol deviations will be removed from the PPAS:

- Subject does not have histologically confirmed diagnosis of melanoma
- Subject does not have unresectable or metastatic melanoma, defined as either
  - Stage IIIB, IIIC, IIID, IVM1a, IVM1b, or IVM1c;

    OR
  - Stage IVM1d with up to 3 cerebral metastases, provided that all lesions have been adequately treated with stereotactic radiation therapy, craniotomy, or gamma knife therapy, with no evidence of progression and not requiring steroids for at least 2 months prior to enrollment.
- Subject is not a candidate for intralesional therapy, and a candidate is defined as either one of the following:
  - At least one injectable cutaneous, subcutaneous, or nodal melanoma lesion equal to or greater than 10 mm in longest diameter;

    OR
  - Multiple injectable melanoma lesions which in aggregate have a longest diameter of equal to or greater than 10 mm

Additionally, the subjects with any of the following important protocol deviations related to prior PD-1 inhibitor use will be removed from the PPAS:

- Subject has not received prior treatment with a PD-1 inhibitor in the adjuvant or metastatic setting (monotherapy or in combination with anti-CTLA-4). Combinations other than anti-PD-1 plus anti-CTLA-4 must have been reviewed with the medical monitor for approval.
- Subject has not received prior anti-PD-1 therapy for at least 2 to 3 consecutive cycles within an 8-week period (based on administration schedule).
- Subject for whom the anti-PD-1 therapy is not the immediate prior line of therapy before enrollment.

The PPAS will be used in the analysis of the select efficacy endpoints.

6.4 Study-specific Analysis Sets

6.4.1 qPCR Suspicious Lesion Swab Analysis Set

The qPCR Suspicious Lesion Swab Analysis Set will include subjects who are in the FAS, receive at least one dose of talimogene laherparepvec, and have at least one swab sample evaluable result from lesions suspicious to be herpetic in origin during the study.

Evaluable samples are sample with either positive, below quantification limit (BQL), or not detected results.

[redacted]

7. Planned Analyses

7.1 Interim Analysis and Early Stopping Guidelines

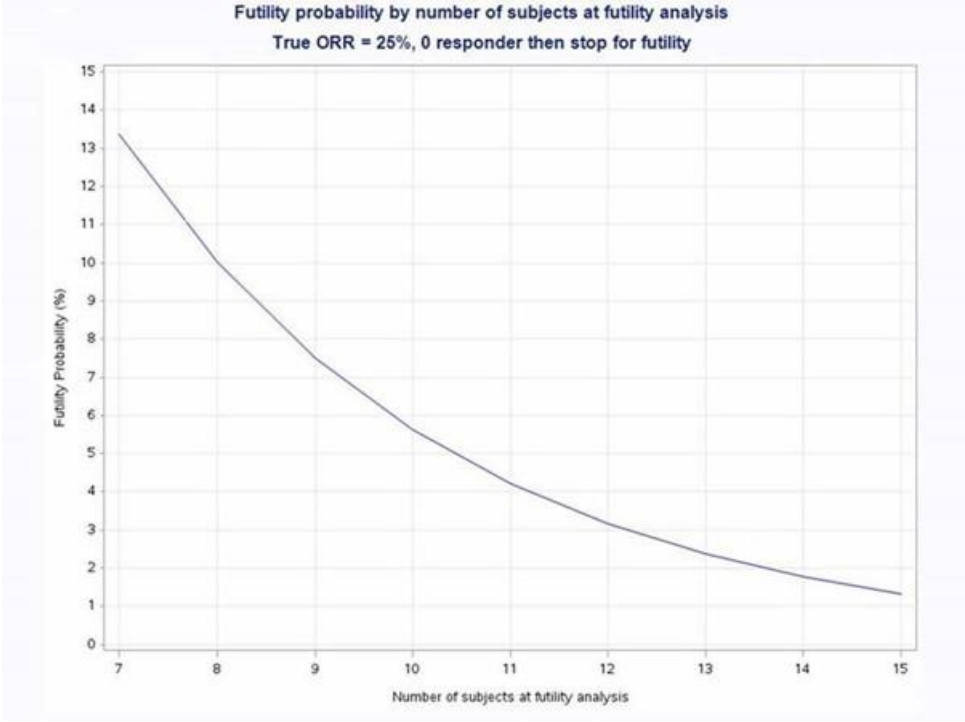
Futility analyses are not planned for cohorts 3 and 4. In cohorts 1 and 2, if there is at least 1 unconfirmed responder (PR/CR as per modified RECIST 1.1) in the first 10

subjects of a cohort, enrollment will continue in that cohort without a futility analysis. Otherwise, the DRT will oversee a futility analysis of unconfirmed response for cohorts 1 and 2, performed separately and only once for each cohort, when 15 subjects within a cohort are evaluable for response (i.e. when 15 subjects have been treated and have had the opportunity to be followed for at least 12 weeks for tumor assessment). Screening in the respective cohort will be paused during the futility analysis. The below table presents the futility criteria:

Number of Evaluable Subjects* at Futility Analysis	Minimum Number of Subjects with an unconfirmed CR/PR to Continue	Probability of Futility (%) True ORR = 25%
15	1	< 5%

* number of subjects treated and who have had the opportunity to be followed for at least 12 weeks for tumor assessment.

When the true response is 25%, the probability of futility is < 5% with at least 1 responder among 15 evaluable subjects.



A data review team (DRT) will review safety data approximately every 3 months until the data snapshot for the primary analysis to ensure no avoidable increased risk for harm to subjects. In addition, the DRT will oversee the futility analysis for each of cohorts 1 and 2. The DRT may request ad hoc meetings at any time. The DRT also has a responsibility to review and evaluate study conduct to determine whether the study integrity may affect the ability of the DRT to fulfill its primary responsibility. Therefore,

the DRT will review and evaluate eligibility/recruitment/retention of participants, management of participants, and adherence to protocol-specified criteria. The DRT will make recommendations concerning the continuation or alteration of the study on the basis of its review of the data.

The DRT will be comprised of an Amgen clinical research medical director, Amgen safety officer, and Amgen biostatistician who are external to the talimogene laherparepvec product team.

Membership, procedures, and meeting timing will be described in the study DRT charter.

7.2 Primary Analysis

The primary analysis will occur when all subjects treated with at least 1 dose of talimogene laherparepvec or pembrolizumab have had the opportunity to be followed for at least 24 weeks for tumor assessment. The database will be cleaned and a locked database will be used for this analysis.

Before the primary analysis, ad hoc analyses may be conducted to support program level activities.

7.3 Final Analysis

The final analysis will occur when all subjects have completed the study. The database will be cleaned and a locked database will be used for this analysis.

8. Data Screening and Acceptance

8.1 General Principles

The objective of the data screening is to assess the quantity, quality, and statistical characteristics of the data relative to the requirements of the planned analyses.

8.2 Data Handling and Electronic Transfer of Data

The Amgen Global Study Operations-Data Management (GSO-DM) department will provide all data to be used in the planned analyses. This study will use the RAVE database.

8.3 Handling of Missing and Incomplete Data

Every effort will be made to obtain complete data in the clinical study. Partial or missing dates of adverse events and concomitant medications will be imputed. Adverse events with missing IP relatedness, seriousness, or CTCAE severity grades are included in TEAE as long as the events qualify for the reporting period. Events with missing relatedness, seriousness, and severity grades will be excluded from treatment-related, serious, and with a CTCAE grade of 3 or higher AE analysis, respectively.

[redacted]

8.4 Detection of Bias

Lack of protocol compliance may introduce potential bias in the estimation of protocol endpoints. All important protocol deviations (IPDs) will be reported, documented and stored in eClinical (a clinical trial management system). IPD reports will be produced [redacted] by the study manager and will be regularly reviewed in the study team's IPD review meetings as well as before analysis.

8.5 Outliers

Descriptive statistics will be used to identify potential outliers in key variables. Suspected outliers will be included in all analyses unless there is sufficient scientific justification to exclude them.

8.6 Distributional Characteristics

All binary endpoints will follow a binomial distribution. The KM estimates for the probability of time-to endpoints are based on non-parametric methods

8.7 Validation of Statistical Analyses

Programs will be developed and maintained, and output will be verified in accordance with current risk-based quality control procedures.

Tables, figures, and listings will be produced with validated standard macro programs where standard macros can produce the specified outputs.

The production environment for statistical analyses consists of Amgen-supported versions of statistical analysis software; for example, the SAS System version 9.4 or later and qualified R.

9. Statistical Methods of Analysis

9.1 General Considerations

Unless otherwise specified, all safety analysis will be performed on the SAS and all efficacy analysis on the FAS. All analyses will be descriptive with no formal hypothesis testing. Analyses will be performed separately for each cohort. In addition, analyses with cohorts pooled together (all cohorts pooled, cohorts 1 and 2 pooled, and cohorts 3 and 4 pooled) will be performed. Cohorts stopped for futility will not be pooled with other cohorts. Cohort data collected on the CRF will be used in the analysis. Cohort data will be checked and reviewed during the study to ensure that subjects are recorded in the correct cohort for analyses prior to database lock.

Continuous variables will be summarized by the non-missing sample size (n), mean, standard deviation, median, first and third quartiles, minimum, and maximum. Categorical variables will be summarized by the n and percentage in each category. Proportions and the corresponding 95% exact CIs will be provided (Clopper and Pearson, 1934). [redacted], time to event endpoints will be summarized with Kaplan-Meier (KM) (Kaplan and Meier, 1958) curves, KM estimates at selected time points, KM quartiles (when estimable), the number of subjects with events and the number of subjects censored. Accompanying 2-sided 95% CI for KM quartiles (Brookmeyer and Crowley, 1982) and KM estimates will be provided.

9.2 Subject Accountability

The number of subjects enrolled will be tabulated by country and investigator site overall and by cohort. Subject disposition (including the number enrolled, treated, ended treatment, ended radiographic follow-up and that completed the safety follow-up visit and the study) will be summarized for all enrolled subjects overall and by cohort. Reasons for ending treatment, ending radiographic follow-up and not completing the 30-day safety follow-up visit will be provided overall and by cohort as well.
Key study dates for the first subject enrolled, last subject enrolled, first subject treated, and last subject's end of study will be presented.

9.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject's initial visit and updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, subcategory codes, and descriptions will be used during the course of the study. Eligibility deviations are defined in the protocol. Eligibility deviations that are defined as IPDs will be summarized in both the IPD and Eligibility Deviation table and IPD and Eligibility Deviation listings.

9.4 Demographic and Baseline Characteristics

Summary statistics of the following demographic and baseline disease characteristics will be tabulated using the Safety Analysis Set for the following:

- Sex (female, male)
- Age at enrolment (<50, ≥50; < 65, ≥ 65; < 75, ≥ 75 years)
- Region (Europe, Non-Europe)
- PD-L1 status (positive, negative, missing/unknown) at baseline
- Disease stage (stage IVM1a or lower, stage IVM1b/c/d) at baseline
- Disease stage (stage IVM1b or lower, stage IVM1c/d) at baseline

- *BRAF*^{V600} mutation at baseline (yes, no)
- LDH (≤ ULN, > ULN; ≤ 2 x ULN, > 2 x ULN)
- ECOG PS (0, 1)
- HSV-1 serostatus at baseline (positive, negative, missing/unknown)
- In-transit disease at baseline (yes, no)
- Prior PD-1 therapy (nivolumab, ipilimumab/nivolumab, pembrolizumab, other)
- Prior anti-cancer therapy and line of therapy for current malignancy
- Prior surgery for current malignancy
- Prior radiotherapy for current malignancy

9.5 Efficacy Analyses

Efficacy analysis will be performed on Full Analysis Set (FAS). Primary analysis for the primary efficacy endpoint as well as the key secondary efficacy endpoints will be repeated for the Per Protocol Analysis Set to assess the impact of IPDs. For key efficacy endpoints, sensitivity analyses excluding subjects who received more than one prior line of anti-PD-1 therapy may be performed. The following sections describe analyses of efficacy endpoints.

9.5.1 Analyses of Primary Efficacy Endpoint(s)

Descriptive statistics for the ORR (CR+PR) will be provided where tumor response evaluations are based on investigator assessments using modified RECIST 1.1.

ORR (CR+PR) will be summarized with associated exact 95% confidence intervals (CIs) for binomial proportions (Clopper & Pearson 1934) (see code fragment in Appendix B).

9.5.2 Analyses of Secondary Efficacy Endpoint(s)

CRR, BOR, DRR and DCR by investigator assessment using modified RECIST 1.1 and iORR, iCRR, iBOR, iDRR and iDCR by investigator assessment using modified irRC-RECIST will be summarized with associated exact 95% CIs for binomial proportions (Clopper & Pearson 1934) (see code fragment in Appendix B).

KM estimates and quartiles for DOR, iDOR, PFS , iPFS, OS and Time to subsequent anti-cancer therapy will be provided (Kaplan and Meier, 1958). KM time to event curves will be presented.

The impact of subsequent anti-cancer therapy on PFS, iPFS and OS will be assessed by censoring at the last evaluable tumor assessment prior to the start of the first subsequent anti-cancer therapy.

9.5.3 Analyses of Exploratory Efficacy Endpoint(s)

9.6 Safety Analyses

9.6.1 Adverse Events

Safety analyses will be conducted separately for each cohort on Safety Analysis Set (SAS). The Medical Dictionary for Regulatory Activities (MedDRA) version 21.1 or later will be used to code all adverse events (AE). The CTCAE version 5.0 or later will be used to grade severity of adverse events.

The subject incidence of AEs will be summarized for all treatment-emergent AEs, serious AEs, AEs leading to withdrawal of investigational product, grade 3 or 4 AEs, fatal AEs, events of interests (EOIs) for talimogene laherparepvec and pembrolizumab events of clinical interest (ECI). Subject incidence of EOI/ECIs will be summarized by the EOI/ECI categories. Preferred terms within each EOI/ECI category will also be summarized.

The subject incidence of all treatment-related AEs, serious AEs, AEs leading to withdrawal of investigational product, grade ≥ 3 AEs, fatal AEs, and EOIs for talimogene laherparepvec will be tabulated by system organ class and preferred term in descending order of frequency.

Summaries of treatment-emergent and serious AEs occurring in at least 5% of the subjects by preferred term will be provided in descending order of frequency.

A Listing will be provided for treatment-emergent adverse events and treatment-emergent serious adverse events. In addition, death on study will be listed.

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

9.6.2 Laboratory Test Results

Laboratory results will be summarized for each cohort with descriptive statistics at baseline and selected time points for selected laboratory parameters. Shifts in grades of selected safety laboratory values between the baseline and the worst on-study value will be tabulated by cohort.

The number and proportion of subjects in each cohort with positive qPCR for talimogene laherparepvec DNA detection in any swab of a lesion suspected to be herpetic in origin will be calculated based on the qPCR Suspicious Lesion Swab Analysis Set.

Individual subjects having a positive qPCR results for talimogene laherparepvec DNA detection will be reviewed.

A listing will be provided for subjects by assessed time point of qPCR analysis results (positive, and numeric value if quantifiable) for talimogene laherparepvec DNA in swab samples taken from cold sore, vesicles, and other lesions suspected to be herpetic in origin.

9.6.3 Vital Signs

Descriptive statistics will be presented for systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature for baseline, each post-baseline visit, change from baseline, and percent change from baseline for each cohort.

9.6.4 Physical Measurements

Physical measurements will not be analyzed.

9.6.5 Electrocardiogram

The electrocardiogram (ECG) measurements from this clinical study were performed as per standard of care for routine safety monitoring, rather than for purposes of assessment of potential QT interval corrected (QTc) effect. Because these evaluations may not necessarily be performed under the rigorous conditions expected to lead to meaningful evaluation of QTc data; neither summaries nor statistical analyses will be provided, and these data would not be expected to be useful for meta-analysis with data from other trials.

9.6.6 Antibody Formation

Baseline HSV-1 serostatus will be summarized. The incidence of HSV-1 seroconversion will be summarized for subjects that are baseline seronegative.

9.6.7 Exposure to Investigational Product

Summary statistics for exposure to talimogene laherparepvec, including total doses administered, total volume administered, duration from the first to the last administration of talimogene laherparepvec, and the average volume received by subject per visit will be provided and will be separated by the first (concentration of 10^6 PFU/ml) and subsequent doses (concentration of 10^8 PFU/ml). Subject incidence rate and reasons for IP delay and dose change/withheld will be tabulated.

Exposure to pembrolizumab including total doses (in mg) administered, relative dose intensity, duration from the first to the last administration, and the average dose received by subject per visit will be provided. Subject incidence rate and reasons for IP delay, IP interruption and dose change/withheld will be examined.

9.6.8 Exposure to Concomitant Medication

The number and proportion of subjects receiving therapies of interest will be summarized by preferred term or category for each cohort as coded by the World Health Organization Drug (WHO DRUG) dictionary.

The number and proportion of subjects receiving subsequent anti-cancer therapies will be summarized by preferred term or category for each cohort as coded by the World Health Organization Drug (WHO DRUG) dictionary.

9.7 Other Analyses

ECOG performance status scores will be summarized at each time point. Changes in scores for ECOG performance status scores from baseline will also be tabulated.

Spider plots for subject-level percent change from baseline in tumor burden by BOR per modified RECIST 1.1 and iBOR per modified irRC-RECIST and disease stage at baseline will be provided. Waterfall plots for subject-level maximum overall tumor burden reduction by BOR per modified RECIST 1.1 and iBOR per modified irRC-RECIST will also be summarized. Tumor assessments occurring after the start of the first subsequent anti-cancer therapy will be excluded from the analysis of tumor burden. With the exception of tumor assessments with an increase of tumor burden ≥ 20% and also demonstrate ≥ 5 mm increase from nadir, tumor assessments occurring on or after the complete or partial removal/reduction of any target lesion with melanoma on pathology evaluation or unknown pathology results will also be excluded from the analysis of tumor burden.

[redacted]

10. Changes From Protocol-specified Analyses

Not applicable.

11. Literature Citations / References

Brookmeyer R and Crowley J. A confidence interval for the median survival time. Biometrics. 1982;38:29-41.

Clopper, C. and Pearson, E. (1934) “The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial,” *Biometrika*, 26, 404–413

Eisenhauer, A., et al (2009) “New Response Evaluation in Solid Tumors: Revised RECIST Guideline (version 1.1)”, EJC, 45, 228-247.

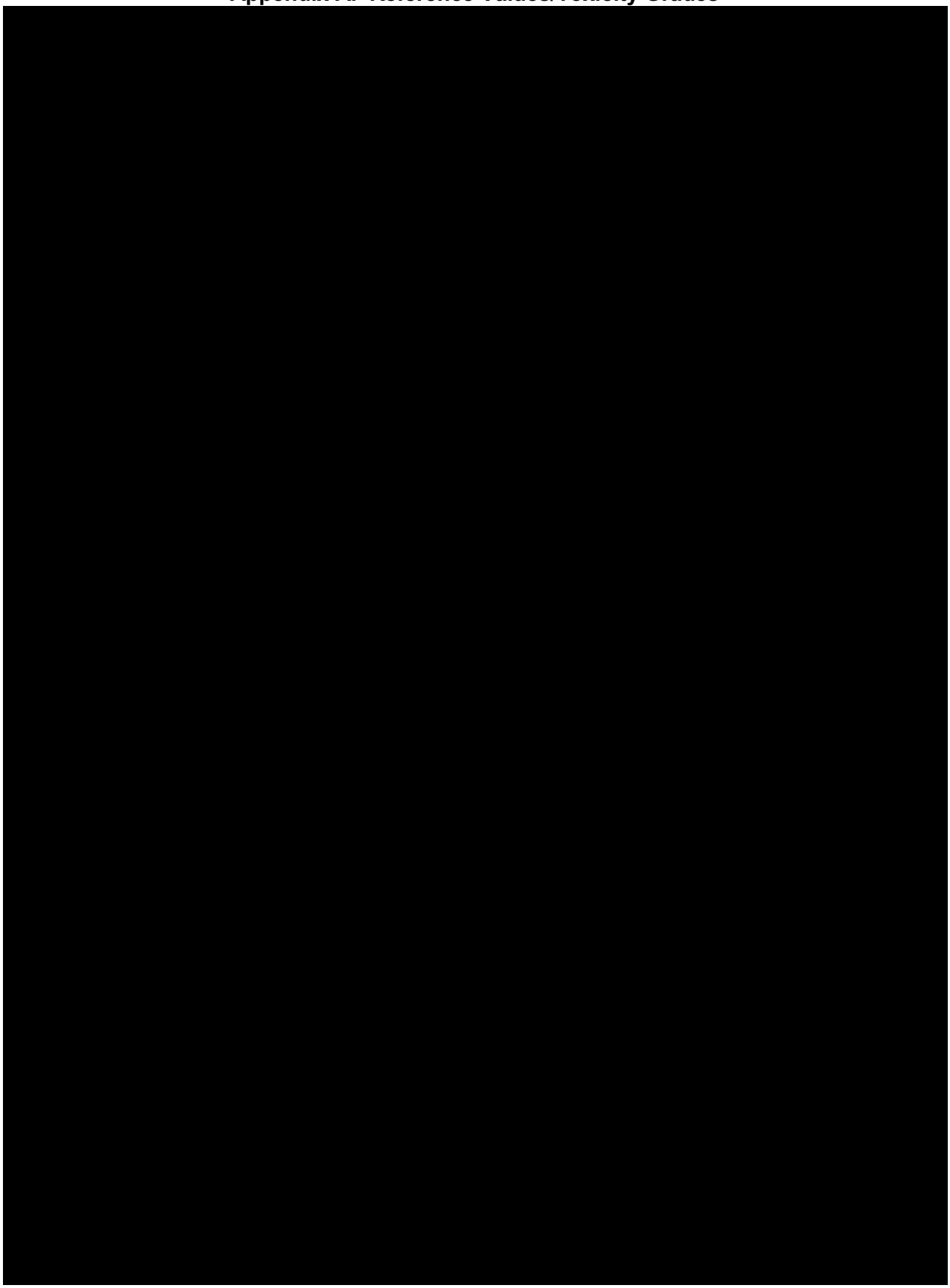
Kaplan EL, Meier P. Nonparametric Estimation from Incomplete Observations. *J Am Stat Assoc*. 1958;53:457-481.

Lin, Guixian, Ying So, and Gordon Johnston. “Analyzing survival data with competing risks using SAS software.” SAS Global Forum. Vol. 2102. 2012.

Pintilie, M. (2006) Competing Risks: A Practical Perspective. Wiley. http://dx.doi.org/10.1002/9780470870709

12. Appendices

Appendix A. Reference Values/Toxicity Grades



Appendix B. Technical Detail and Supplemental Information Regarding Statistical Procedures and Programs

B.1 Clopper-Pearson Exact Confidence Interval

```
proc freq data=data1;
tables var1/ binomial(exact);
run;
```

B.2 Non-parametric cumulative incidence function (CIF)

```
proc lifetest data=event_data outcif=cif plots=cif(test);
time timevar*cnsr(1)/eventcode=0;
ods output;
run;
```

Variable cnsr:

Value 0 = [redacted] progression event

1 = censored

2 = competing risk event