STATISTICAL ANALYSIS PLAN

A Phase 1b/3 Multicenter, Randomized Trial of Talimogene Laherparepvec in Combination With Pembrolizumab for the Treatment of Subjects With Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck

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Table of Abbreviations

Abbreviation or Term	Definition/Explanation
AE	adverse event
AEOSI	**adverse events of specific interest**
BDSG	Biomedical Data Stewardship Governance
BOR	best overall response (per RECIST v1.1)
CI	confidence interval
CR	complete response (per RECIST v1.1)
CRF	case report form
CRR	complete response rate (per RECIST v1.1)
CSR	Clinical Study Report
CST	Clinical Study Team
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate (per RECIST v1.1)
DILI	drug-induced liver injury
DLRT	Dose Level Review Team
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response (per RECIST v1.1)
DRE	disease-related event
EAS	Efficacy Analysis Set
ECG	electrocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOI	event of interest
FAS	Full Analysis Set
FDA	Food and Drug Administration
GSO-DM	Amgen Global Study Operations-Data Management
HPV	Human papillomavirus
HR	hazard ratio
HSV, HSV-1	herpes simplex virus, herpes simplex virus type 1
IP	Investigational product
IPD	Important protocol deviation
iBOR	best overall response (per irRECIST)
iCR	complete response (per irRECIST)

Abbreviation or Term	Definition/Explanation
iCRR	complete response rate (per irRECIST)
iDCR	disease control rate (per irRECIST)
iDOR	duration of response (per irRECIST)
iORR	objective response rate (per irRECIST)
iPD	progressive disease (per irRECIST)
iPFS	progression-free survival (per irRECIST)
iPR	partial response (per irRECIST)
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors (RECIST)
iSD	stable disease (per irRECIST)
iUE	unable to evaluate (per irRECIST)
IV	intravenous
IVR	Interactive Voice Response
KM	Kaplan-Meier
L-CR	lesion complete response
L-ORR	lesion objective response rate
L-PR	lesion partial response
LSE(G)	global last subject enrolled
MRI	magnetic resonance imaging
ND	not done
ORR	objective response rate (per RECIST v1.1)
OS	overall survival
PD	progressive disease (per RECIST v1.1)
PD-L1	programmed cell death-1 ligand 1
PFS	progression-free survival (per RECIST v1.1)
PFU	plaque-forming unit
PK	pharmacokinetics
PR	partial response
qPCR	quantitative polymerase chain reaction
rcd	rapid clinical deterioration
RECIST	Response Evaluation Criteria in Solid Tumor
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SCCHN	squamous cell carcinoma of the head and neck
SD	stable disease (per RECIST v1.1)

Abbreviation or Term	Definition/Explanation
UE	unable to evaluate (per RECIST v1.1)
WHO DRUG	World Health Organization Drug

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 amendment #4 for Talimogene Laherparepvec Study 20130232 dated 11 May 2018. The scope of this plan includes the primary analysis**,** follow-up analysis, and final analysis of the phase 1b part of the study that are planned and will be executed by the Biostatistics department unless otherwise specified.

The clinical study report (CSR) will be written based on the results of the primary completion analysis, follow-up analysis, and final analysis of phase 1b. Data collected and analyzed in Amgen-owned databases and systems will adhere to approved Data Element Standards and International Case Report Form (CRF) Standards established by Biomedical Data Stewardship Governance (BDSG).

2. Objectives

2.1 Primary

Phase 1b

- To evaluate the safety, as assessed by incidence of dose limiting toxicity (DLT), of talimogene laherparepvec in combination with pembrolizumab in subjects with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN)

2.2 Secondary

Phase 1b

- To evaluate the efficacy of talimogene laherparepvec in combination with pembrolizumab as assessed by:
  - Objective response rate (iORR), complete response rate (iCRR), and best overall response (iBOR); duration of response (iDOR), disease control rate (iDCR), and progression free survival (iPFS) (response evaluation by investigator using immune-related RECIST [irRECIST])
  - OS
- To evaluate the safety of talimogene laherparepvec in combination with pembrolizumab as assessed by incidence of adverse events and laboratory abnormalities

2.3 Exploratory

Phase 1b

- To evaluate ORR, CRR, BOR, DCR, and DOR (response by investigator using modified RECIST v1.1)
- To evaluate responses in injected and uninjected tumors by investigator assessment
- To estimate the incidence of detection of talimogene laherparepvec DNA in lesions suspected to be herpetic in origin

- To estimate the incidence of clearance of talimogene laherparepvec DNA from blood and urine
- To estimate the rate of detection and subject incidence of talimogene laherparepvec DNA and virus from blood, urine exterior of occlusive dressing, surface of injected lesions and oral mucosa
- To assess blood and tumor tissue for potential biomarkers which predict and/or are correlated with clinical outcomes to talimogene laherparepvec with pembrolizumab

3. Study Overview

3.1 Study Design

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

3.1.1 Phase 1b Study Design

Phase 1b is a multicenter single-arm study. Talimogene laherparepvec will be administered in combination with pembrolizumab to approximately 40 subjects with recurrent or metastatic SCCHN. DLT will be evaluated based on the first 18 DLT-evaluable subjects. An expansion cohort of up to an additional 22 treated subjects will be enrolled to obtain a total of approximately 40 treated subjects to further evaluate the safety and to estimate the efficacy of the combination of talimogene laherparepvec with pembrolizumab to support a decision to initiate the phase 3 study.

3.1.1.1 Rules for DLT Evaluation in Phase 1b

Safety will be evaluated considering the incidence of DLTs among all DLT-evaluable subjects in the phase 1b. See protocol Section 3.1.1.1 for rules for DLT evaluation and Section 3.1.1.2 for the definition of DLT.

3.1.2 Tumor Response Assessment

For Phase 1b, conventional RECIST 1.1 (Eisenhauer et al., 2009), with the following modification, will be used by the investigator to determine eligibility:

- Increased total target lesions to a maximum of 10 (up to a maximum of 5 per organ)

A variation of RECIST 1.1, irRECIST, will be used by the investigator to assess tumor response and make treatment decisions, and to assess the secondary tumor response related endpoints in the phase 1b portion of the study.

3.1.3 Follow-Up

3.1.3.1 Follow-Up Analysis for Phase 1b

For the phase 1b part of the study, the primary analysis will be repeated 1 year after the last subject enrolled.

3.1.3.2 Safety Follow-up

All subjects who receive investigational product will complete a safety follow-up visit approximately 30 (+7) days after the last dose of study treatment. Adverse events and disease related events (DRE) will be collected as described in protocol Section 9.2. Serious adverse events and any concomitant medications associated with serious adverse events observed by the investigators or reported by the subjects that occur through 90 (+7) days after the cessation of all study treatment or 30 (+7) days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, will be reported to Amgen and recorded in the CRF.

3.1.3.3 Long-term Follow-up

After the safety follow-up visit, all subjects will enter the long-term follow-up. Subjects will be followed for survival and subsequent anticancer therapies every 12 weeks (± 28 days) from safety follow-up for approximately 36 months after the last subject is enrolled (see section 7.3). In addition, talimogene laherparepvec/placebo related adverse events that occur through the end of the long-term follow-up will be reported. The phase 1b subjects will be followed for approximately 36 months after the last subject is enrolled.

For subjects who discontinue study treatment without documented iPD and have not initiated a new anticancer therapy, every effort should be made to continue monitoring tumor response status by clinical and radiographic tumor assessments.

3.2 Sample Size

3.2.1 Sample Size Considerations for Phase 1b

See protocol Section 10.2.1.

4. Study Endpoints and Covariates

4.1 Study Endpoints

4.1.1 Primary Endpoints

Phase 1b

- Subject incidence of DLT

4.1.2 Secondary Endpoints

Phase 1b

- iORR (iCR+iPR), iCRR, iBOR, iDOR, iDCR, and iPFS (response evaluation by investigator using irRECIST)
- OS
- Subject incidence of treatment-emergent and treatment-related adverse events (all adverse events, grade ≥ 3 adverse events, serious adverse events, fatal adverse events, adverse events and serious adverse events leading to discontinuation of treatment, and adverse events defined as events of interest) and laboratory abnormalities.

4.1.3 Exploratory Endpoints

- Phase 1b
  - ORR, CRR, BOR, DCR, and DOR (response evaluation by investigator using modified RECIST v1.1)
  - Incidence of clearance of talimogene laherparepvec DNA from blood and urine
  - Rate of detection and subject incidence of talimogene laherparepvec DNA and virus from blood, urine, exterior of occlusive dressing, surface of injected lesions, and oral mucosa
  - Response rates in injected and uninjected lesions: evaluable lesion incidence of a ≥ 30% decrease in lesion length for ≥ 4 weeks
  - Incidence of detection of talimogene laherparepvec DNA in lesions suspected to be herpetic in origin
  - Potential biomarkers which predict and/or are correlated with clinical outcomes to talimogene laherparepvec and pembrolizumab

4.2 Planned Covariates

To explore the robustness of efficacy signal in phase 1b, **i**ORR may also be estimated separately by PD-L1 status (positive/not positive) or other covariates listed below.

- Region (South America vs North America vs EU vs Asia vs Other for phase 1b)
- Age at baseline: < 50, ≥ 50; < 65, ≥ 65; < 75, ≥ 75 years
- Sex (female vs male)
- Prior smoking (never vs former vs current)
- HSV-1 serostatus (positive vs negative)

- HPV status (positive vs negative vs unknown) (phase 1b)
- The sum of diameters of target lesions
- Weight loss >5% in the previous 6 months
- Primary tumor site (oral cavity vs oropharynx vs hypopharynx vs larynx)
- Brain metastasis status (baseline brain metastasis vs no baseline brain metastasis)
- Prior radiotherapy for the treatment of SCCHN
- Extent of disease (metastatic vs locoregionally recurrent)
- Prior lines of therapy in recurrent/metastatic setting (0, 1 or 2)
- PD-L1 status at baseline (PD-L1 positive vs PD-L1 not positive)
- CD8+ T cell density
- Maximum blinded investigational product total volume per treatment administration > 4 mL at highest concentration (yes, no)

Other covariates reported in the literature or from other Amgen studies maybe considered as appropriate at the time of analysis.

5. Hypotheses and/or Estimations

Phase 1b:

Talimogene laherparepvec in combination with pembrolizumab will be safe and well tolerated in subjects with recurrent or metastatic SCCHN.

6. Definitions

1-year, 2-year, and 3-year survival

The Kaplan-Meier (KM) estimate of the overall survival (OS) at 1 year, 2 years, and 3 years.

Actual Follow-Up Time

Actual follow-up time for a subject is calculated from the enrollment (phase 1b) date to the last on-study date (ie, death date, or date last known to be alive for subjects still alive).

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 (ie, on or prior to the first date of dosing) in the respective phase of the study. Parameters that are obtained on the same day as the first date of dosing are assuming to be pre-dose. For subjects who are not dosed, the

baseline value of a parameter is considered to be the latest value prior to the enrollment date.

Best overall response (iBOR) per irRECIST

Best overall response (iBOR) of complete response (iCR), partial response (iPR), stable disease (iSD), progressive disease (iPD) or unevaluable (iUE) will be derived based on investigator assessment using immune-related RECIST [irRECIST]) (see protocol Appendix D). The visit overall response assessments occurring after initiation of non-study anticancer therapy **will not be included. The visit overall response assessments occurring on or after** a complete or partial removal/reduction of any target or non-target lesion containing cancer or with unknown pathology results will not be included **except an iPD observation**.

Confirmation of iCR, iPR, and iPD is required as noted in the individual definitions for iCR, iPR and iPD per irRECIST. 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 56 days **after the date of first dose** (phase 1b) or an unconfirmed iPD when confirmation of iPD is required (eg, initial iPD without clinical deterioration). As indicated in Table 1, iBOR is defined as the best overall visit response in the following order: iCR, iPR, iSD, iPD, or iUE.

Table 1. Matrix of Determining iBOR per irRECIST

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, * *,iCR, iPR,*	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 ≥ 56 days from first dose (phase 1b); however, this is not required for an unconfirmed iCR/iPR.
*, iPD, iPD, * *, iPDrcd, * *, iPD, non-iPD, iPD,* iPDrcd = iPD from rapid clinical deterioration as the reason for ending radiographic follow-up.	iPD, iPD iPD,iSD,iPD,iPD iPD, iUE, iPD iPDrcd	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 there is rapid clinical deterioration; iPDrcd does not require confirmation. If an initial visit overall response of iPD is not confirmed, then a subsequent iPD does not need to be confirmed for a subject overall response of iPD.
*, iSD, * iPD	iSD iUE, iSD iPD iUE, iPD	iUE	Criteria for iBOR=iCR, iPR, iSD, or iPD not met. iSD must be < 56 days from first dose (phase 1b).

Best overall response (BOR) per RECIST v1.1

Best overall response (BOR) of complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD) or unevaluable (UE) will be derived based on investigator assessment using RECIST v1.1 (see protocol Appendix E). The visit overall response assessments occurring after initiation of non-study anticancer therapy **will not be included. The visit overall response assessments occurring on or after** a complete or partial removal/reduction of any target or non-target lesion containing cancer or with unknown pathology results will not be included **except a PD observation**.

Confirmation of CR and PR is not required. For the derivation of BOR, the overall visit response will be UE if SD is earlier than 56 days **after the date of first dose**. As indicated in protocol Table 15, BOR is defined as the best overall visit response in the following order: CR, PR, PD, SD, or UE.

BOR per modified RECIST v1.1 for Phase 1b subjects will follow the same derivation.

Disease control rate (iDCR) per irRECIST

Disease control rate (iDCR) per irRECIST is defined as the incidence of an iBOR of iCR or iPR or iSD among the set of subjects analyzed.

Disease control rate (DCR) per RECIST v1.1

Disease control rate (DCR) per RECIST v1.1 is defined as the incidence of a BOR of CR or PR or SD among the set of subjects analyzed.

Duration of response (iDOR) per irRECIST

Duration of response (iDOR) per irRECIST is defined as the time from the date of an initial response of iCR or iPR that is subsequently confirmed to the earlier of a subject overall response of iPD (see protocol Table 14) or death. Subjects who have not ended their response at the time of analysis will have iDOR censored at their last evaluable tumor assessment. This endpoint only applies to subjects with an iCR or iPR per irRECIST.

Duration of response (DOR) per RECIST v1.1

Duration of response (DOR) per RECIST v1.1 is defined as the time from the date of an initial response of CR **or** PR to the earlier of a subject overall response of PD (see protocol Table 16) or death. Subjects who have not ended their response at the time of

analysis will have DOR censored at their last evaluable tumor assessment. This endpoint only applies to subjects with a CR or PR per RECIST v1.1.

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 purposes of final collection of data for the primary endpoint(s), for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early.

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

Primary Completion Phase 1b only: The time when the last phase 1b subject is assessed or receives an intervention for the purposes of final collection of data for the primary endpoint of phase 1b. The primary completion is anticipated to occur when the last phase 1b subject completes the week 9 tumor response assessment.

End of Study (end of trial): The end of study date is defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable. This is anticipated to occur 36 months after the last subject is enrolled.

Evaluable tumor assessment

A visit overall response other than unevaluable (iUE) for irRECIST (see protocol Table 14) or not evaluable (NE) for RECIST v1.1 (see protocol Table 16).

Event of Interest (EOI) for Talimogene Laherparepvec

An event of interest (EOI) is a noteworthy treatment-emergent adverse event for **talimogene laherparepvec** that may warrant careful monitoring. It could be serious or non-serious, and could include events that might be potential precursors or prodromes for more serious medical conditions in susceptible individuals (Council for International Organizations of Medical Sciences (CIOMS) VI, 2005). [redacted]. The set of EOIs to be evaluated will be identified at the time of analysis based on the current

product-specific standard MedDRA queries **or Amgen MedDRA Queries** maintained by Amgen Pharmacovigilance Operations.

Investigational product (IP)

Investigational product (IP) refers to talimogene laherparepvec (also known as "Amgen IP") and pembrolizumab (also known as "non-Amgen IP").

Lesion complete response (L-CR)

Lesion complete response (L-CR) applies only to measurable lesions (baseline) and is defined as complete disappearance of a lesion with confirmation by a repeat consecutive assessment no less than 4 weeks (28 days) from the date first documented. A lesion will be censored for L-CR after the start of non-study anticancer therapy, if it merges with another lesion or it is resected (except if it is completely resected and pathology indicates absence of malignant cells).

Lesion objective response rate (L-ORR)

Lesion objective response rate (L-ORR) is defined as the incidence among a set of lesions analyzed of L-CR or L-PR. Lesions without a follow-up assessment will be regarded as a non-responding lesion.

Lesion partial response (L-PR)

Lesion partial response applies only to measurable lesions (baseline) and is defined as ≥ 30% decrease in lesion length (ie, longest diameter for non-nodal, shortest axis for nodal) relative to baseline with confirmation by a repeat consecutive assessment no less than 4 weeks (28 days) from the date first documented. A lesion will be censored for L-PR after the start of non-study anticancer therapy, if it merges with another lesion or it is resected (except if it is completely resected and pathology indicates absence of malignant cells).

Objective response rate (iORR) per irRECIST

iORR is defined as the incidence of an iBOR of iCR or iPR per irRECIST among a set of subjects analyzed. Subjects with an iCR or iPR will be defined as responders. Subjects who do not have any follow-up tumor assessments will be regarded as non-responders per irRECIST.

Objective response rate (ORR) per RECIST v1.1

ORR is defined as the incidence of a BOR of CR or PR per RECIST v1.1 among a set of subjects analyzed. Subjects with a CR or PR will be defined as responders. Subjects who do not have any follow-up tumor assessments will be regarded as non-responders per RECIST v1.1.

Overall Survival (OS)

OS is defined as the interval from first dose (phase 1b) to the event of death from any cause; otherwise, OS is censored at the date the subject was last known to be alive. Subjects with a vital status (alive or dead) obtained after the data cut off will be censored at the date cutoff date.

Pembrolizumab Adverse Events of Special Interest (AEOSI)

AEOSI for pembrolizumab are immune-mediated events and infusion-related reactions, which represent the known risks for and are considered causally associated with, pembrolizumab. A pre-specified list of preferred terms (PTs) based on MedDRA was developed by Merck to consistently characterize the nature and frequency of each AEOSI across the clinical program, regardless of causality as reported by investigators. These PTs are considered to be medically equivalent to the identified risks for pembrolizumab.

Pembrolizumab Event of Clinical Interest (ECI)

Pembrolizumab Events of Clinical Interest include: an overdose of pembrolizumab as defined in protocol Section 9.6, and potential drug-induced liver injury (DILI) from pembrolizumab as defined in protocol Section 9.7.

Potential Follow-Up Time

Potential follow-up time for a subject is calculated from the enrollment (phase 1b) date to the analysis data cutoff date.

Progression-free survival (iPFS) per irRECIST

Progression-free survival (iPFS) per irRECIST is defined as the interval from first dose (phase 1b) to the earlier of a subject overall response of iPD (see protocol Table 14) or death from any cause; otherwise, iPFS is censored at the last evaluable tumor assessment. The initial date of an iPD that is consecutively confirmed will be the iPFS date.

Progression-free survival (PFS) per RECIST v1.1

Progression-free survival (PFS) per RECIST v1.1 is defined as the interval from first dose (phase 1b) to the earlier of a subject overall response of PD (see protocol Table 16) or death from any cause; otherwise, PFS is censored at the last evaluable tumor assessment.

Safety Follow-up Visit

Safety follow-up visit will be performed approximately 30 (+7) days after the last dose of IP. In addition, serious adverse events will be reported that occur through 90 (+7) days after the cessation of all study treatment or 30 (+7) days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier.

Serious Adverse Events (SAE)

Serious adverse events (SAE) are defined as any adverse event categorized as serious as determined by investigator per protocol Section 9.1.3.

Study day

Study day is calculated from the first day IP is administered (ie, non-zero dosing) to the subject. Study day = visit date – first dose date +1 if visit date is on or after the first dose date. Study day = visit date – first dose date, if visit date is before the first dose date.

Study Day 1

Study day 1 is defined as the first day of IP administration (ie, non-zero dosing) of the IP after enrollment. The day prior to Study Day 1 is considered Day -1.

Study Week 0

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

Treatment period

Treatment period is defined as the period between the first IP dose date and 30 days after the last IP dose date.

Treatment-emergent Adverse Events (TEAE)

Treatment-emergent adverse events (TEAE) are defined as any adverse event with an onset date during the treatment period, **through 30 days after the last dose of talimogene laherparepvec or pembrolizumab, whichever is later**. Adverse events

that occur on the same day as the first dose date of IP 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 talimogene laherparepvec and the question "Did event start before first dose of IP" is answered "Yes" on eCRF, then the event will not be counted as a treatment-emergent AE. Additionally, if an event is identified as disease-related on the eCRF, it will not be counted as a treatment-emergent AE).

Treatment-emergent Disease-Related Events (DREs)

Treatment-emergent Disease-Related Events (DREs) are defined as events determined by the investigator to be disease-related, with an onset during the treatment period**, through 30 days after the last dose of talimogene laherparepvec or pembrolizumab, whichever is later**. DREs that occur on the same day as the first dose of IP 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 talimogene laherparepvec and the check box indicating prior to the first dose of IP is checked on the eCRF, then the event will not be counted as a treatment-emergent DRE).

Treatment-emergent Serious Adverse Events (TESAE)

Treatment-emergent serious adverse events (TESAE) are defined as any SAE with an onset date during the treatment period through 90 days after the last dose of talimogene laherparepvec or pembrolizumab, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. SAEs that occur on the same day as the first dose date of IP will be treated as treatment-emergent SAE unless indicated otherwise (for example, if an event occurs on the same date as the first administration of talimogene laherparepvec and the question "Did event start before first dose of IP" is answered "Yes" on eCRF, then the event will not be counted as a treatment-emergent SAE. Additionally, if an event is identified as disease-related on the eCRF, it will not be counted as a treatment-emergent SAE).

7. Analysis Subsets

7.1 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 dosing of study treatment and have received at least 2 doses of talimogene laherparepvec and 2 doses of

pembrolizumab in combination, or have a DLT during the DLT evaluation period after at least 1 dose of talimogene laherparepvec and pembrolizumab in combination.

7.2 Efficacy Analysis Set

The Efficacy Analysis Set (EAS) will be used for the primary efficacy analysis of the phase 1b. It is a subset of the Safety Analysis Set where subjects with locoregionally advanced disease with a recurrence < 3 months after prior platinum-containing curatively intended multimodal therapy are excluded.

7.3 Full Analysis Set

Secondary efficacy analyses for the phase 1b part of the study will be conducted on the Full Analysis Set (FAS) defined as all subjects who have received at least 1 dose of talimogene laherparepvec and 1 dose of pembrolizumab in combination. Efficacy will be analyzed with the FAS overall and excluding subjects in the EAS.

7.4 Safety Analysis Set

The Safety Analysis Set (SAS) will include all enrolled subjects (phase 1b) who received at least 1 dose of talimogene laherparepvec or pembrolizumab.

7.5 Biomarker Analysis Set

A Biomarker Analysis Set will be defined separately for each individual candidate biomarker. For exploratory and predictive analyses, the analysis set will include all treated (phase 1b) subjects with a baseline biomarker result and, for analyses of biomarker changes, the analysis set will include all treated (phase 1b) subjects that have a baseline and at least one subsequent biomarker result.

7.6 qPCR Suspicious Lesion Swab Analysis Set

The qPCR Suspicious Lesion Swab Analysis Set will include subjects who are enrolled (phase 1b), receive at least one dose of talimogene laherparepvec / placebo, 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, BQL, or not detected results.

7.7 qPCR Blood Analysis Set

The qPCR Blood Analysis Set applies only to the phase 1b and will include treated subjects that have at least one post-dose blood sample evaluable result for qPCR testing of talimogene laherparepvec DNA.

7.8 qPCR Urine Analysis Set

The qPCR Urine Analysis Set applies only to the phase 1b and will include treated subjects that have at least one post-dose urine sample evaluable result for qPCR testing of talimogene laherparepvec DNA.

7.9 qPCR Exterior Occlusive Dressing Analysis Set

The qPCR Exterior Occlusive Dressing Analysis Set applies only to the phase 1b and will include treated subjects that have at least one post-dose exterior occlusive dressing surface swab evaluable result for qPCR testing of talimogene laherparepvec DNA.

7.10 qPCR Injected Lesion Analysis Set

The qPCR Injected Lesion Analysis Set applies only to the phase 1b and will include treated subjects that have at least one post-dose swab of an injected lesion with an evaluable result for qPCR testing of talimogene laherparepvec DNA.

7.11 qPCR Oral Mucosa Analysis Set

The qPCR Oral Mucosa Analysis Set applies only to the phase 1b and will include treated subjects that have at least one post-dose swab of oral mucosa with an evaluable result for qPCR testing of talimogene laherparepvec DNA.

7.12 qPCR Blood Clearance Analysis Set

The qPCR Blood Clearance Analysis Set applies only to the phase 1b and will include treated subjects that have at least one qPCR positive talimogene laherparepvec DNA blood sample, and at least one evaluable subsequent sample at any time during the same cycle.

7.13 qPCR Urine Clearance Analysis Set

The qPCR Urine Clearance Analysis Set applies only to the phase 1b and will include treated subjects that have at least one qPCR positive talimogene laherparepvec DNA urine sample, and at least one evaluable subsequent sample at any time during the same cycle.

7.14 Lesion Analysis Sets

The Injected Lesion Analysis Set includes any target lesion that was ever injected and the Uninjected Lesion Analysis Set includes any target lesion that was never injected. The Injected Lesion Evaluable and Uninjected Lesion Evaluable analysis sets will include the corresponding subset of target lesions with at least one post-baseline measurement prior to a censoring event, ie, non-study anticancer therapy, merged with another lesion, or resection (except if it is completely resected and pathology indicates

absence of malignant cells). If a lesion splits, the sum of the length of the split lesions will be added together prior to analysis.

8. Interim Analysis and Early Stopping Guidelines

8.1 Interim Analyses

DLT interim safety analyses are planned and conducted by the study team for the phase 1b with data being reviewed by a DLRT.

8.1.1 DLT Safety Analysis (Phase 1b)

Up to 3 planned safety interim analyses will occur during the phase 1b to evaluate the incidence of DLT according to timing/rules described in protocol Table 1 (Section 3.1.1). At each interim analysis, a DLT listing will be generated. The number and percentage of subjects with DLTs will be tabulated in a summary table among DLT-evaluable subjects. DLT evaluations will be based on the DLT Analysis Set. Data will be reviewed by a DLRT.

9. Data Screening and Acceptance

9.1 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.

9.2 Data Handling and Electronic Transfer of Data

The Amgen Global Study Operations-Data Management (GSO-DM) department will provide all data, with the exception of biomarker data, to be used in the planned analyses. This study will use the RAVE database. PD-L1 and HPV data will be transferred electronically to Amgen via secure server.

9.3 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 and disease-related events (DRE) with missing IP relatedness (AEs only), seriousness, or CTCAE severity grades will be included in analyses as long as the events qualify for the reporting period. Events with missing relatedness (AEs only), seriousness, or severity grades will be excluded from corresponding treatment-related, serious, and worst grade analyses, respectively. If an AE or DRE end date is completely missing and the death date is available, the end date will be imputed with the death date. Details of the imputation algorithm for partial or missing dates, including death dates, are provided in [redacted] Section 13.

9.4 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 using Cognos by the study manager and will be regularly reviewed in the study team's IPD review meetings as well as before analysis.

9.5 Outliers

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

9.6 Distributional Characteristics

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

Time to event endpoints will be evaluated with the non-parametric log-rank test.

9.7 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.

10. Statistical Methods of Analysis

10.1 General Principles

For the phase 1b part of the study, the DLT Analysis Set will be used to summarize the subject incidence of DLT and, unless specified otherwise, the SAS will be used for all analyses of safety. Safety may also be analyzed using the EAS. The primary analysis of efficacy for the phase 1b will be based on the EAS with secondary analyses based on the FAS overall and excluding subjects in the EAS.

In principle, summary statistics including mean, standard deviation, median, first and third quartiles, will be provided for continuous variables. Frequency and percentage will be summarized by treatment arm for binary and categorical variables. Proportions and the corresponding 95% confidence intervals will be based on normal approximations and

the treatment comparison will be based on a Cochran-Mantel-Haenszel test. Exact tests will be considered for subgroup analyses when the cell size is considered small.

Time to-event endpoints will be estimated using the KM method.

Descriptive statistics will be provided for efficacy, safety, talimogene laherparepvec DNA, and biomarker endpoints as appropriate

10.2 Subject Accountability

The number of subjects enrolled will be tabulated by countries and investigator sites overall and by treatment group (when applicable). Subject disposition (including the number screened, enrolled, treated, ended treatment, ended radiographic follow-up, and that completed the safety follow-up visit) will be summarized separately for all enrolled subjects in phase 1b. Subject accountability will be tabulated by respective treatment group when applicable. Reasons for not receiving treatment, for ending treatment, endpoint radiographic follow-up, and not completing the 30-day safety follow-up visit will be provided.

10.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject's visit and updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, sub-category 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.

10.4 Demographic and Baseline Characteristics

Summary statistics of the following demographic and baseline characteristics will be tabulated using the SAS for phase 1b of the study.

- Region (South America vs North America vs EU vs Asia vs Other for phase 1b; South America vs North America vs EU vs Japan vs Other Asia vs Other for phase 3)
- Age at baseline: < 50, ≥ 50; < 65, ≥ 65; < 75, ≥ 75 years
- Sex (female vs. male)
- Prior smoking (never vs former vs current)
- HSV-1 serostatus (positive vs negative)
- The sum of diameters of target lesions
- Weight loss > 5% in the previous 6 months

- Primary tumor site (oral cavity vs oropharynx vs hypopharynx vs. larynx)
- Brain metastasis status (baseline brain metastasis vs no baseline brain metastasis)
- Prior radiotherapy for treatment of SCCHN
- Extent of disease (metastatic vs locoregionally recurrent)
- Prior lines of therapy in recurrent/metastatic setting (0, 1 or 2)
- PD-L1 status at baseline (positive versus not positive)
- CD8+ T cell density
- HPV (HPV- negative vs HPV-positive vs unknown)
- ECOG performance status (0 vs 1)
- Maximum blinded investigational product total volume per treatment administration > 4 mL at highest concentration (yes, no)

10.5 Efficacy Analyses

10.5.1 Analyses of Primary Efficacy Endpoint(s)

10.5.1.1 Phase 1b

The subject incidence of DLT will be summarized using the DLT Analysis Set.

10.5.2 Analyses of Secondary Efficacy Endpoints

10.5.2.1 Phase 1b

The primary analysis of efficacy for the phase 1b will be based on the EAS, with secondary analysis based on the FAS overall and excluding subjects in the EAS. All endpoints of the phase 1b will be descriptively analyzed.

The main efficacy endpoint in the phase 1b for the phase 3 decision will be the iORR with or without confirmation of response. Given the observed **i**ORR in the Efficacy Analysis Set, the Bayesian posterior probability will be calculated that the true combination **i**ORR exceeds the expected ORR for pembrolizumab by an absolute amount (delta). The expected **i**ORR for pembrolizumab in the study population with 9 weeks minimum potential follow-up is approximately 11% and will be represented by a beta(2.2,17.8) distribution with mean 0.11 and precision 20.0. The iORR for the combination will be represented by a beta(0.2,1.8) distribution with mean 0.11 and precision 2.0. Given the observed iORR, the posterior probability will be calculated for a delta increase from 0% to 30% in 5% increments as well as a 90% credible region for delta (see [redacted]).

10.5.3 Analyses of Exploratory Endpoints

10.5.3.1 Phase 1b

The exploratory analysis for Phase 1b for ORR, CRR, BOR, DCR, and DOR (response by investigator using modified RECIST v1.1) will be analyzed using the analysis methods described in **the first paragraph of** Section 10.5.2.1 above, where applicable.

- Response rates in injected and uninjected lesions:
  L-ORR and the incidence of L-PR and L-CR separately at the lesion level will be summarized by enrolled/randomized treatment for subjects in the EAS (phase 1b) and FAS(G)(phase 3) for the Injected Lesion Analysis Set and the Uninjected Lesion Analysis Set separately, and also for the corresponding evaluable analysis sets. Waterfall plots for the maximum percent decrease in the lesion diameter will also be provided. The number of subjects will be provided with at least one lesion in each analysis as well as the distribution of the number of lesions per subject. The subject incidence of an L-CR or L-PR and each individually will also be summarized separately for subjects with a lesion included in the Injected Lesion and Uninjected Lesion analysis sets and corresponding evaluable analysis sets.

10.5.4 Biomarker Endpoints

The analysis of biomarkers for other exploratory objectives will be described and reported separately.

Phase 1b

- Potential biomarkers which predict and/or are correlated with clinical outcomes to talimogene laherparepvec and pembrolizumab

10.5.5 Sensitivity Analyses

The Bayesian analyses of phase 1b efficacy in Section 10.5.2.1 may be repeated to assess sensitivity due to the choice of prior for pembrolizumab and/or to account for new external results, such as from KEYNOTE-040.

10.6 Safety Analyses

Safety analyses will be conducted separately for phase 1b based on the SAS analysis sets, as follows.

10.6.1 Adverse Events and Disease-Related Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 or later will be used to code all adverse events (AE) and disease-related events (DRE) to a system

organ class and a preferred term. The CTCAE version 4.0 will be used to grade severity of adverse events. In general, events with missing IP relatedness (AEs only), seriousness, or CTCAE severity grades will be included in the analysis as long as the event is considered treatment-emergent. However, analyses of treatment-related (AEs only), SAE, or grade 3 or higher, or combinations thereof will exclude events with missing relatedness, seriousness, and severity grades, respectively.

The analyses for AEs will include TEAEs unless otherwise specified. The subject incidence of TEAEs will be summarized for all AEs, SAEs, AEs leading to withdrawal of investigational product, grade 3 or **higher** AEs, fatal AEs, talimogene laherparepvec events of interest (EOI), pembrolizumab events of clinical interest (ECI), **and pembrolizumab adverse event of specific interest (AEOSI).**

Preferred term **and worst grade within each category of EOI (including treatment-emergent EOIs and treatment-related EOIs), EOI SAEs (including treatment-emergent EOIs SAE and treatment-related EOI SAEs), AEOSI (including treatment-emergent AEOSIs and treatment-related AEOSIs) and AEOSI SAE (including treatment-emergent AEOSI SAEs and treatment-related AEOSI SAEs)** will be summarized.

The subject incidence of all TEAEs, SAEs, AEs leading to withdrawal of investigational product, grade 3 or **higher** AEs, and fatal AEs will be tabulated by system organ class, preferred term in descending order of frequency **and worst grade**.

Summaries of **all TEAEs, SAEs, AEs leading to withdrawal of investigational product, grade 3 or higher AEs, fatal AEs, treatment-related AEs**, TEAEs and SAEs occurring in at least 1% of the subjects by preferred term in any treatment arm will be provided in descending order of frequency.

Sensitivity analyses of TEAEs, **SAEs, AE leading to withdrawal of investigational product and fatal AEs** will be conducted, considering any DRE as an AE.

Subject incidence of DREs**, serious DREs, DREs leading to withdrawal of investigational product** and fatal DREs will be tabulated by system organ class, preferred term, **and worst grade. Summaries of DREs, serious DREs, and DREs leading to withdrawal of investigational product and fatal DREs will be tabulated by preferred term.**

Including all the preferred terms, a comparison of all TEAEs side by side to the TEAE/TEDRE and a comparison of all TESAEs side by side to the

TESAE/TESDREs will be produced, sorting by system organ class, preferred term, and worst grade.

A listing of fatal AEs and fatal DREs will be provided. **A listing of SAEs and SAE for EOIs will be provided.** Listing of SAEs from consent and before first dose of study therapy will also be provided separately.

A listing of treatment-related AEs reported in long term follow-up will be provided for the final CSR and may be analyzed earlier as part of a program-wide analysis.

Potential or known unintended exposure to Talimogene Laherparepvec, related suspected signs or symptoms, and detection of Talimogene Laherparepvec DNA in swabs of suspected herpetic-like lesions in a subject's household member, caregiver, or healthcare provider will be reported in the final CSR. Individual reported cases with available qPCR testing results will be reviewed. Additionally, unintended exposures will be analyzed periodically as part of a program-wide analysis.

10.6.2 Laboratory Test Results

Shifts in grades of safety laboratory values between the baseline and the worst on-study value will be tabulated. Subject incidence of potential hepatotoxicity as identified by the Hy's Law criteria (FDA guidance for Industry Drug Induced Liver Injury: pre-marketing evaluation, July 2009) as well as confirmed DILI events as reported by investigators will be presented.

10.6.3 Vital Signs

Analysis of vital signs will not be performed as routine monitoring and collection of vital sign data is not sufficient to require an analysis.

10.6.4 Electrocardiogram (ECG)

The ECG measurements from this clinical study will performed as per standard of care for routine safety monitoring. Summaries and statistical analyses of ECG measurements are not planned.

10.6.5 Antibody Formation

The incidence and percentage of subjects who develop anti-pembrolizumab antibodies (binding and if positive, neutralizing) at any time and at last post baseline assessment will be analyzed by Merck.

10.6.6 Exposure to Investigational Product

Summary statistics for exposure to talimogene laherparepvec, including total doses administered, total volume administered, distribution of the number of administrations

with a total volume > 4 mL, 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 and reasons for IP 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, dose change/withheld dose delay, and dose interruption of pembrolizumab will be examined.

A listing of the unique manufacturing lot numbers, and a listing of the subjects administered each manufacturing lot number will be provided.

10.6.7 Exposure to Concomitant Medication

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

10.6.8 Talimogene Laherparepvec DNA

10.6.8.1 Incidence of Detection of Talimogene Laherparepvec DNA in Lesions Suspected to be Herpetic in Origin

Phase 1b

The number and proportion of subjects 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. An exact 95% CI for the binomial proportion will be calculated (Clopper & Pearson, 1934).

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

10.6.8.2 Incidence of Clearance of Talimogene Laherparepvec DNA From Blood and Urine

Phase 1b

The number and proportion of subjects with undetectable talimogene laherparepvec DNA per qPCR among subjects with sample collected in each cycle will be presented. Incidence of clearance of talimogene laherparepvec DNA from Cycle 1, 2, 3, and 4 will

be calculated by cycle. An exact 95% CI for the binomial proportion will be calculated (Clopper & Pearson, 1934).

Analysis of incidence of clearance of talimogene laherparepvec DNA from blood and urine will be analyzed using the qPCR Blood Clearance Analysis Set and qPCR Urine Clearance Analysis Set, respectively.

10.6.8.3 Rate of Detection and Subject Incidence of Talimogene laherparepvec DNA and Virus From Blood, Urine, Exterior of Occlusive Dressing, Surface of Injected Lesions, and Oral Mucosa

Phase 1b

Rate of detection and subject incidence of talimogene laherparepvec DNA and virus will be analyzed separately for blood, urine, exterior of occlusive dressing, surface of injected lesions, and oral mucosa using qPCR Blood Analysis Set, qPCR Urine Analysis Set, qPCR Exterior Occlusive Dressing Analysis Set, qPCR Injected Lesion Analysis Set, and qPCR Oral Mucosa Analysis Set, respectively.

The number and proportion of subjects who have at least 1 positive qPCR result will be presented. The number and proportion of subjects exhibiting detectable virus from TCID50 assay will also be presented. Numeric results of positive qPCR, and separately for detectable virus from TCID50, will be summarized as a continuous variable. An exact 95% CI for the binomial proportion will be calculated (Clopper & Pearson, 1934).

Subject incidence and rate of subsequent positive TCID50 testing for positive qPCR testing results will be presented using qPCR Exterior Occlusive Dressing Analysis Set, qPCR Injected Lesion Analysis Set, and qPCR Oral Mucosa Analysis Set.

qPCR and TCID50 results for subjects having a positive qPCR testing will be reviewed.

10.7 Pharmacokinetic or Pharmacokinetic/Pharmacodynamic Analysis

Pembrolizumab PK sample and data analysis will be provided by Merck.

Pembrolizumab concentrations and pharmacokinetic (PK) parameters including the C_{min}, C_{max}, and AUC will be listed and summarized using descriptive statistics. Preliminary analysis will include examining the PK parameters for extreme values falling out of the standardized ranges of deviations as predicted by the existing population PK model. The impact of any outliers on the results of the analyses will be evaluated. Population PK analysis, based on pharmacokinetic PK data obtained in this study together with that obtained from other studies, will be conducted.

The analysis plan and report from that population PK analysis will be described in separate documents.

11. Changes From Protocol-specified Analyses

Following the review of the phase 1b primary analysis of efficacy and safety, a decision was made by the sponsor to not proceed with the phase 3 portion of this study. Therefore, all study design and statistical methods related to the phase 3 that are described in the protocol are not included in this SAP. None of the phase 3 analyses specified in the protocol will be performed.

12. Literature Citations / References

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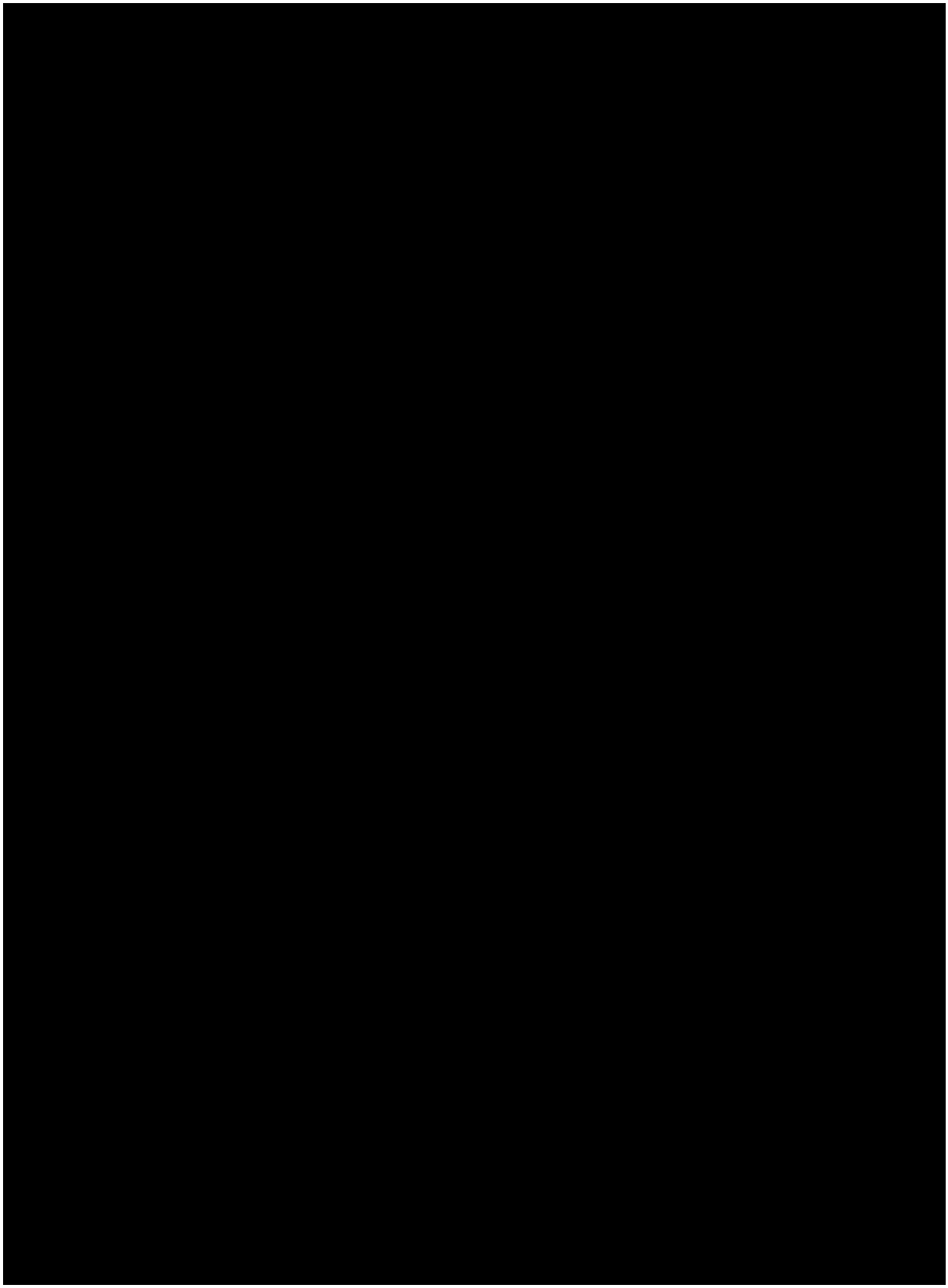
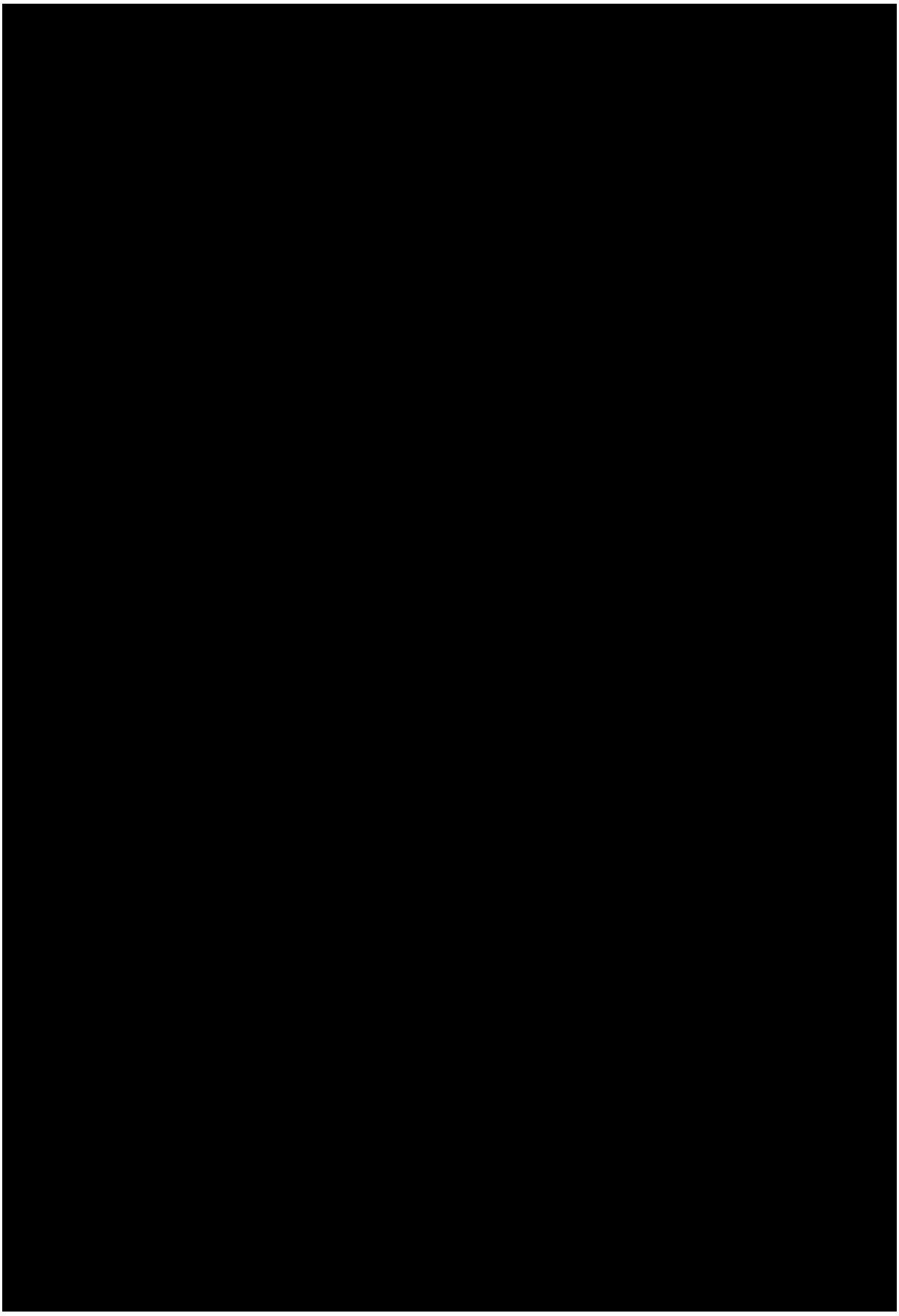
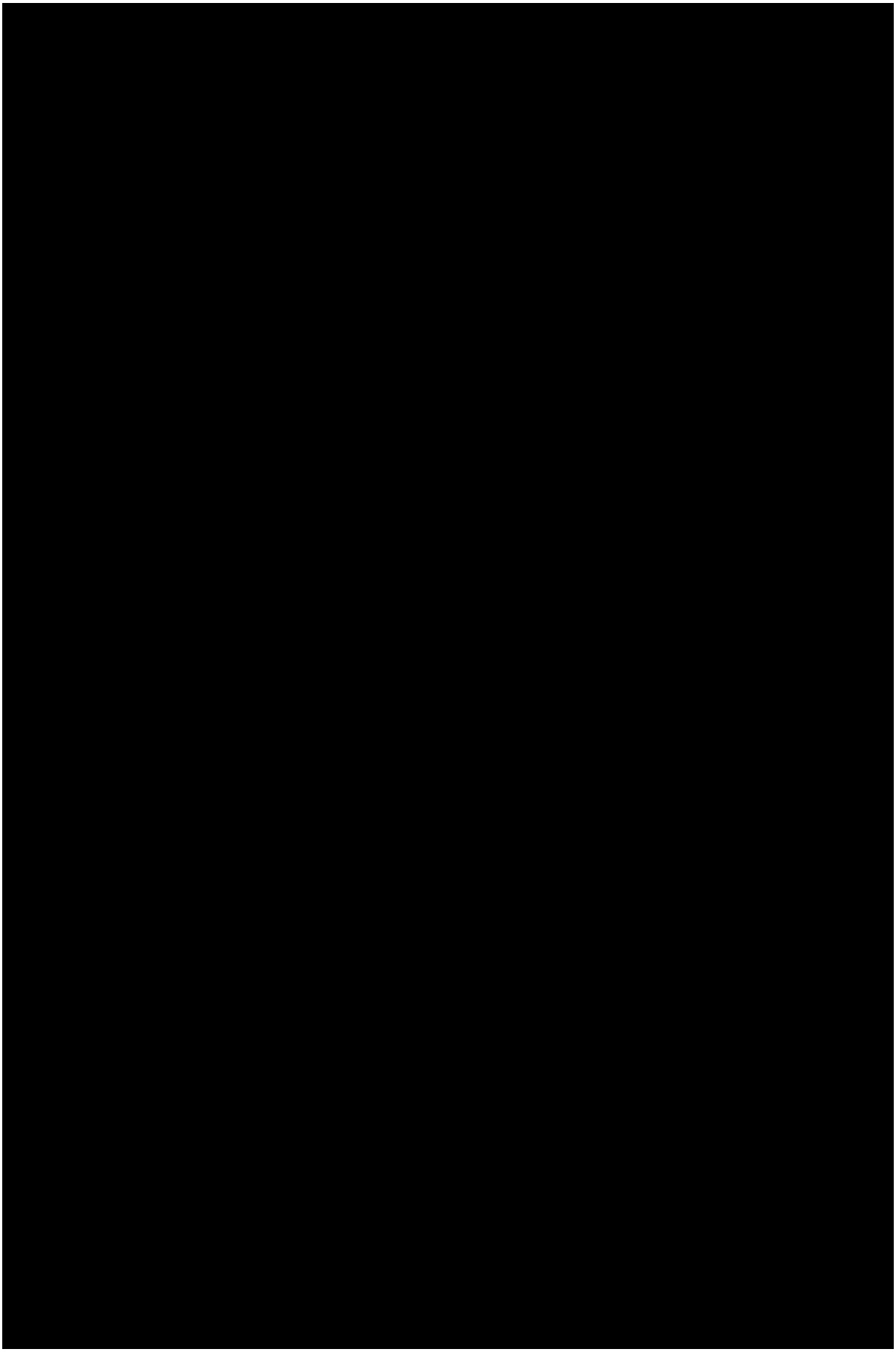
Eisenhauer, A., et al. (2009) New Response Evaluation in Solid Tumors: Revised RECIST Guideline (version 1.1). *EJC*, **45**, 228-247.

13. Appendices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