Clinical trial results:
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

Summary

EudraCT number	2015-003011-38
Trial protocol	GB AT ES GR DE PT FR PL
Global end of trial date	28 August 2020

Results information

Result version number	v1 (current)
This version publication date	02 September 2021
First version publication date	02 September 2021

Trial information

Trial identification

Sponsor protocol code	20130232

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02626000
WHO universal trial number (UTN)	-
Other trial identifiers	Merck Study ID: KEYNOTE-137, Acronym: MASTERKEY-232

Notes:

Sponsors

Sponsor organisation name	Amgen Inc.
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, CA, United States, 91320
Public contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com
Scientific contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 August 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 August 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the safety, as assessed by incidence of dose limiting toxicity (DLT), of talimogene laherparepvec in combination with pembrolizumab in adults with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN).

Protection of trial subjects:

This study was conducted in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines.
The study protocol and all amendments, the informed consent form, and any accompanying materials provided to the subjects were reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) at each study center.
The investigator or his/her designee informed the subject of all aspects pertaining to the subject's participation in the study before any screening procedures were performed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 April 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	36 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Greece: 1
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	Switzerland: 10
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	United States: 4
Country: Number of subjects enrolled	Australia: 2
Worldwide total number of subjects	36
EEA total number of subjects	8

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	21
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 19 centers in Australia, Canada, Europe, and the United States.
This study was designed to be conducted in 2 parts (phase 1b and phase 3). A decision was made not to initiate the phase 3 part of the study.

Pre-assignment

Screening details:

From April 2016 to August 2017, 36 patients with histologically confirmed diagnosis of metastatic or recurrent SCCHN were enrolled into this study. The first 16 patients were dose-limiting toxicity (DLT) evaluable and constituted the DLT analysis set. Twenty additional patients were enrolled to further evaluate safety and estimate efficacy.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Talimogene Laherparepvec + Pembrolizumab

Arm description:

Talimogene laherparepvec was administered by intralesional injection into injectable cutaneous, subcutaneous, and nodal lesions at an initial dose of 10 plaque-forming units (PFU) per mL on day 1 followed by a dose of 10^8 PFU/mL every 3 weeks (Q3W) thereafter. Pembrolizumab was administered by intravenous infusion at a dose of 200 mg Q3W. Participants were treated until complete response, no injectable lesions, confirmed disease progression, intolerance of study treatment, 24 months from the date of the first dose of talimogene laherparepvec, or end of study, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Talimogene laherparepvec
Investigational medicinal product code	
Other name	IMLYGIC®
Pharmaceutical forms	Solution for injection
Routes of administration	Intralesional use

Dosage and administration details:

The initial dose of talimogene laherparepvec was up to 8.0 mL of 10 PFU/mL. Subsequent doses of talimogene laherparepvec were up to 8.0 mL of 10^8 PFU/mL.

Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	KEYTRUDA®
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered as a 30-minute intravenous infusion at a dose of 200 mg Q3W

Number of subjects in period 1	Talimogene Laherparepvec + Pembrolizumab
Started	36
Completed	6
Not completed	30
Adverse event, serious fatal	29
Decision by Sponsor	1

Baseline characteristics

Reporting groups

Reporting group title	Talimogene Laherparepvec + Pembrolizumab

Reporting group description:

Talimogene laherparepvec was administered by intralesional injection into injectable cutaneous, subcutaneous, and nodal lesions at an initial dose of 10 plaque-forming units (PFU) per mL on day 1 followed by a dose of 10^8 PFU/mL every 3 weeks (Q3W) thereafter. Pembrolizumab was administered by intravenous infusion at a dose of 200 mg Q3W. Participants were treated until complete response, no injectable lesions, confirmed disease progression, intolerance of study treatment, 24 months from the date of the first dose of talimogene laherparepvec, or end of study, whichever occurred first.

Reporting group values	Talimogene Laherparepvec + Pembrolizumab	Total	
Number of subjects	36	36	
Age Categorical Units: participants			
< 65 years	21	21	
≥ 65 years	15	15	
Age Continuous Units: years			
arithmetic mean	60.8		
standard deviation	± 10.8	-	
Sex: Female, Male Units: participants			
Female	7	7	
Male	29	29	
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	1	1	
Black (or African American)	1	1	
Native Hawaiian or Other Pacific Islander	0	0	
White	33	33	
Other	1	1	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	2	2	
Not Hispanic or Latino	34	34	
Unknown or Not Reported	0	0	
Eastern Cooperative Oncology Group (ECOG) Performance Status			
A scale to assess a patient's disease status. 0 = Fully active, able to carry out all pre-disease performance without restriction; 1 = Restricted in physically strenuous activity, ambulatory and able to carry out work of a light nature; 2 = Ambulatory and capable of all self-care, unable to carry out any work activities. Up and about > 50% of waking hours; 3 = Capable of only limited self-care, confined to bed or chair > 50% of waking hours; 4 = Completely disabled, confined to bed or chair; 5 = Dead.			
Units: Subjects			
0 (Fully active)	9	9	
1 (Restricted but ambulatory)	27	27	
Herpes Simplex Virus Status			

Units: Subjects			
Negative	5	5	
Positive	22	22	
Unknown	9	9	
Primary Tumor Site Units: Subjects			
Oropharynx	9	9	
Larynx	4	4	
Oral Cavity	20	20	
Hypopharynx	3	3	

End points

End points reporting groups

Reporting group title	Talimogene Laherparepvec + Pembrolizumab

Reporting group description:

Talimogene laherparepvec was administered by intralesional injection into injectable cutaneous, subcutaneous, and nodal lesions at an initial dose of 10 plaque-forming units (PFU) per mL on day 1 followed by a dose of 10^8 PFU/mL every 3 weeks (Q3W) thereafter. Pembrolizumab was administered by intravenous infusion at a dose of 200 mg Q3W. Participants were treated until complete response, no injectable lesions, confirmed disease progression, intolerance of study treatment, 24 months from the date of the first dose of talimogene laherparepvec, or end of study, whichever occurred first.

Primary: Number of Participants with a Dose Limiting Toxicity (DLT)

End point title	Number of Participants with a Dose Limiting Toxicity (DLT)[1]

End point description:

The following toxicities (graded per CTCAE 4.0) were considered DLTs if judged by the investigator as related to either study drug:
-grade 4 non-hematologic toxicity;
-≥ grade 3 pneumonitis;
-grade 3 non-hematologic toxicity for >3 days with optimal supportive care (grade 3 fatigue of any duration was not a DLT);
-any ≥ grade 3 non-hematologic laboratory value if medical intervention or hospitalization was required, or the abnormality persisted at ≥ grade 3 for >1 week unless deemed not clinically important by investigator and sponsor;
-grade 3 or 4 febrile neutropenia;
-thrombocytopenia < 25 x 10/L associated with bleeding event requiring intervention;
-serious herpetic events;
-death;
-other intolerable toxicity leading to discontinuation of either study drug.
The DLT analysis set included subjects who had the opportunity to be on treatment for >6 weeks and had received > 2 doses of both study drugs in combination, or who had a DLT after >1 dose of both study drugs in combination.

End point type	Primary

End point timeframe:

First 6 weeks after the initial administration of talimogene laherparepvec and pembrolizumab in combination

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This was a single arm study, no statistical comparisons were performed.

End point values	Talimogene Laherparepvec + Pembrolizumab			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: participants	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate

End point title	Objective Response Rate

End point description:

Objective response rate was defined as the percentage of participants with a best overall response of complete response (iCR) or partial response (iPR) assessed by the investigator using immune-related Response Evaluation Criteria in Solid Tumors (irRECIST). Response was assessed by computed tomography (CT) or magnetic resonance imaging (MRI).
iCR: Disappearance of all lesions (whether measurable or not and whether baseline or new). Any pathological lymph nodes (target or non-target) must have reduction in short axis to <10 mm.
iPR: Decrease in tumor burden ≥ 30% relative to baseline.
Confirmation of response required a confirmatory scan at least 4 weeks after first indication of response.
The efficacy analysis set included enrolled participants who received at least 1 dose of talimogene laherparepvec or pembrolizumab, and excluded participants with locoregionally advanced disease with a recurrence < 3 months after prior platinum-containing curatively intended multimodal therapy.

End point type	Secondary

End point timeframe:

Up to the primary analysis data cutoff date of 02 November 2017; median (minimum, maximum) time on follow-up was 14.36 (1.4, 67.0) weeks.

End point values	Talimogene Laherparepvec + Pembrolizumab			
Subject group type	Reporting group			
Number of subjects analysed	32			
Units: percentage of participants				
number (confidence interval 95%)				
Confirmed Response	9.4 (2.0 to 25.0)			
Unconfirmed Response	15.6 (5.3 to 32.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Response Rate

End point title	Complete Response Rate

End point description:

Complete response rate (iCRR) was defined as the percentage of participants with a best overall response of complete response assessed by the investigator using immune-related Response Evaluation Criteria in Solid Tumors (irRECIST). Response was based on the size of tumors assessed by computed tomography (CT) or magnetic resonance imaging (MRI).
Complete response (iCR): Disappearance of all lesions (whether measurable or not and whether baseline or new) and confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented was required. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Analyses are presented below for both the unconfirmed and confirmed results conducted using for the efficacy analysis set.

End point type	Secondary

End point timeframe:

Up to the primary analysis data cutoff date of 02 November 2017; median (minimum, maximum) time on follow-up was 14.36 (1.4, 67.0) weeks.

End point values	Talimogene Laherparepvec + Pembrolizumab			
Subject group type	Reporting group			
Number of subjects analysed	32			
Units: percentage of participants				
number (confidence interval 95%)				
Confirmed Response	0.0 (0.0 to 10.9)			
Unconfirmed Response	0.0 (0.0 to 10.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Confirmed Response

End point title	Best Overall Confirmed Response

End point description:

Best overall response of iCR, iPR, stable disease (iSD), progressive disease (iPD) or unevaluable (iUE) based on investigator assessment per irRECIST.
iCR: Disappearance of all lesions (whether measurable or not and whether baseline or new). Any pathological lymph nodes (target or non-target) reduced in short axis to <10 mm.
iPR: Decrease in tumor size ≥ 30% relative to baseline.
iPD: Increase in tumor size ≥ 20% and at least 5 mm increase compared to nadir or qualitative worsening of non-target lesions or a new lesion.
iSD: Neither sufficient shrinkage to qualify for iCR or iPR nor sufficient increase to qualify for iPD.
iUE: Any baseline lesion which was not assessed or was unable to be evaluated leading to an inability to determine the status of that particular tumor.
Not Done: Radiographic imaging was not performed to evaluate response.
iCR, iPR, and iPD required confirmation by a consecutive scan at least 4 weeks after first documentation.
The efficacy analysis set was used.

End point type	Secondary

End point timeframe:

Up to the primary analysis data cutoff date of 02 November 2017; median (minimum, maximum) time on follow-up was 14.36 (1.4, 67.0) weeks.

End point values	Talimogene Laherparepvec + Pembrolizumab			
Subject group type	Reporting group			
Number of subjects analysed	32			
Units: participants				
Complete Response (iCR)	0			
Partial Response (iPR)	3			
Stable Disease (iSD)	10			

Progressive Disease (iPD)	4			
Unevaluable (iUE)	6			
Not Done	9			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Confirmed Response

End point title	Duration of Confirmed Response

End point description:

Duration of response (iDOR) per irRECIST was defined as the time from the date of an initial response of iCR or iPR that was subsequently confirmed to the earlier of a participant overall response of iPD or death. Participants who did not end their response at the time of analysis were censored at their last evaluable tumor assessment.
The analysis was conducted in the efficacy analysis set subjects with a best response of iCR or iPR.
"99999" indicates values that could not be estimated.

End point type	Secondary

End point timeframe:

Up to the primary analysis data cutoff date of 02 November 2017; median (minimum, maximum) time on follow-up was 14.36 (1.4, 67.0) weeks.

End point values	Talimogene Laherparepvec + Pembrolizumab			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate

End point title	Disease Control Rate

End point description:

Disease control rate (iDCR) was defined as the percentage of participants with a best overall response of iCR or iPR or iSD assessed by the investigator using irRECIST.
Complete response (iCR): Disappearance of all lesions (whether measurable or not and whether baseline or new) and confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented was required. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial response (iPR): Decrease in tumor burden ≥ 30% relative to baseline. Confirmation by a consecutive assessment at least 4 weeks after first documentation required.
Stable disease (iSD): Neither sufficient shrinkage to qualify for iCR or iPR nor sufficient increase to qualify for iPD.

Analyses are presented below for both the unconfirmed and confirmed results.
The efficacy analysis set was used.

End point type	Secondary

End point timeframe:

Up to the primary analysis data cutoff date of 02 November 2017; median (minimum, maximum) time on follow-up was 14.36 (1.4, 67.0) weeks.

End point values	Talimogene Laherparepvec + Pembrolizumab			
Subject group type	Reporting group			
Number of subjects analysed	32			
Units: percentage of participants				
number (confidence interval 95%)				
Confirmed Response	40.6 (23.7 to 59.4)			
Unconfirmed Response	40.6 (23.7 to 59.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival

End point title	Progression Free Survival

End point description:

Progression-free survival (iPFS) per irRECIST was defined as the interval from first dose to the earlier of a participant overall response of iPD or death from any cause; otherwise, iPFS was censored at the last evaluable tumor assessment. The initial date of an iPD that was consecutively confirmed was used.
The efficacy analysis set was used.

End point type	Secondary

End point timeframe:

Up to the primary analysis data cutoff date of 02 November 2017; median (minimum, maximum) time on follow-up was 14.36 (1.4, 67.0) weeks.

End point values	Talimogene Laherparepvec + Pembrolizumab			
Subject group type	Reporting group			
Number of subjects analysed	32			
Units: months				
median (confidence interval 95%)	3.0 (2.0 to 6.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival (OS) was defined as the interval from first dose to the event of death from any cause; otherwise, OS was censored at the date the participant was last known to be alive.
The efficacy analysis set was used.

End point type	Secondary

End point timeframe:

Up to the primary analysis data cutoff date of 02 November 2017; median (minimum, maximum) time on follow-up was 14.36 (1.4, 67.0) weeks.

End point values	Talimogene Laherparepvec + Pembrolizumab			
Subject group type	Reporting group			
Number of subjects analysed	32			
Units: months				
median (confidence interval 95%)	5.2 (2.1 to 11.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events

End point title	Number of Participants with Adverse Events

End point description:

The severity of adverse events was assessed by the investigator according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, and based on the following scale:
Grade 1 = mild,
Grade 2 = moderate,
Grade 3 = severe,
Grade 4 = life-threatening,
Grade 5 = death.
A serious adverse event is an AE that met at least 1 of the following serious criteria:
• fatal;
• life threatening;
• required in-patient hospitalization or prolongation of existing hospitalization;
• resulted in persistent or significant disability/incapacity;
• congenital anomaly/birth defect;
• other medically important serious event.
The analysis includes enrolled participants in phase 1b who received at least 1 dose of talimogene laherparepvec or pembrolizumab.

End point type	Secondary

End point timeframe:

From first dose of study drug to 30 days after last dose; the median (range) duration of treatment was 5.6 (0.1 to 75.3) weeks for talimogene laherparepvec and 6.1 (0.1, 105.3) weeks for pembrolizumab.

End point values	Talimogene Laherparepvec + Pembrolizumab			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: participants				
All treatment-emergent adverse events	36			
Treatment-emergent adverse events grade ≥ 2	36			
Treatment-emergent adverse events grade ≥ 3	26			
Treatment-emergent adverse events grade ≥ 4	11			
Serious adverse events	26			
AE leading to discontinuation of T-VEC	6			
AE leading to discontinuation of pembrolizumab	6			
Fatal adverse events	7			
Talimogene laherparepvec-related AEs	21			
Pembrolizumab-related AEs	21			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug to 30 days after last dose; the median (range) duration of treatment was 5.6 (0.1 to 75.3) weeks for talimogene laherparepvec and 6.1 (0.1, 105.3) weeks for pembrolizumab.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Talimogene Laherparepvec + Pembrolizumab

Reporting group description:

Talimogene laherparepvec was administered by intralesional injection into injectable cutaneous, subcutaneous, and nodal lesions at an initial dose of 10 plaque-forming units (PFU) per mL on day 1 followed by a dose of 10^8 PFU/mL every 3 weeks (Q3W) thereafter. Pembrolizumab was administered by intravenous infusion at a dose of 200 mg Q3W.
Participants were treated until complete response, no injectable lesions, confirmed disease progression, intolerance of study treatment, 24 months from the date of the first dose of talimogene laherparepvec, or end of study, whichever occurred first.

Serious adverse events	Talimogene Laherparepvec + Pembrolizumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	26 / 36 (72.22%)		
number of deaths (all causes)	29		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma of head and neck			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Tumour pain			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tumour haemorrhage			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Vascular disorders			
Arterial haemorrhage			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	1 / 1		
Hypotension			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Mucosal haemorrhage			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			

subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia aspiration			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Respiratory arrest			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Stridor			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Delirium			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Toxicity to various agents			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Tracheal obstruction			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tracheostomy malfunction			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Somnolence			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebral venous sinus thrombosis			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Odynophagia			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatitis			

subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal pain			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intervertebral disc protrusion			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal chest pain			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Localised infection			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Pneumonia			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Staphylococcal infection			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tracheitis			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wound infection			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wound infection bacterial			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			

Decreased appetite			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypercalcaemia			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Euglycaemic diabetic ketoacidosis			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Talimogene Laherparepvec + Pembrolizumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 36 (91.67%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	3 / 36 (8.33%)		
occurrences (all)	3		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	5 / 36 (13.89%)		
occurrences (all)	7		
Face oedema			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Fatigue			

subjects affected / exposed	10 / 36 (27.78%)		
occurrences (all)	12		
Influenza like illness			
subjects affected / exposed	5 / 36 (13.89%)		
occurrences (all)	16		
Injection site pain			
subjects affected / exposed	3 / 36 (8.33%)		
occurrences (all)	4		
Pyrexia			
subjects affected / exposed	12 / 36 (33.33%)		
occurrences (all)	18		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 36 (19.44%)		
occurrences (all)	7		
Dyspnoea			
subjects affected / exposed	12 / 36 (33.33%)		
occurrences (all)	14		
Haemoptysis			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	3		
Orthopnoea			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Productive cough			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Increased bronchial secretion			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Insomnia			

subjects affected / exposed occurrences (all)	4 / 36 (11.11%) 4		
Investigations Body temperature increased subjects affected / exposed occurrences (all) Weight decreased subjects affected / exposed occurrences (all)	 3 / 36 (8.33%) 5 2 / 36 (5.56%) 2		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	 6 / 36 (16.67%) 6		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	 6 / 36 (16.67%) 6		
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	 3 / 36 (8.33%) 4		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Dysphagia subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Odynophagia subjects affected / exposed occurrences (all)	 9 / 36 (25.00%) 11 5 / 36 (13.89%) 6 8 / 36 (22.22%) 13 7 / 36 (19.44%) 7 3 / 36 (8.33%) 9		

Oral pain			
subjects affected / exposed	4 / 36 (11.11%)		
occurrences (all)	4		
Stomatitis			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	3		
Vomiting			
subjects affected / exposed	5 / 36 (13.89%)		
occurrences (all)	7		
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	3 / 36 (8.33%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	3 / 36 (8.33%)		
occurrences (all)	3		
Neck pain			
subjects affected / exposed	4 / 36 (11.11%)		
occurrences (all)	4		
Pain in extremity			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	4 / 36 (11.11%)		
occurrences (all)	5		
Oral candidiasis			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	3		
Rhinitis			

subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Skin infection			
subjects affected / exposed	3 / 36 (8.33%)		
occurrences (all)	3		
Upper respiratory tract infection			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	5 / 36 (13.89%)		
occurrences (all)	8		
Hypokalaemia			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 June 2016	The following key changes were incorporated into protocol amendment 1: • Updated key contacts • Changed phase 3 portion of study to be double-blind and added placebo to the pembrolizumab arm. • Reordered sections to separate phase 1b and phase 3 in the synopsis, and general study procedures sections in order to more clearly delineate which sections are specific to each phase of the study. Additionally, to reduce the number of footnotes, reorganized Section 7 to provide more description to study procedures. • Updated background information for talimogene laherparepvec and pembrolizumab to reflect recent publications or presentations and approvals. • Updated biopsy requirements in inclusion criteria • Removed biodistribution and shedding at select sites in phase 3 as we will have sufficient data from phase 1 • Removed PD-L1 status as a stratification factor • Removed registry study option • Updated contraception language for exclusion criterion and also sections related to pembrolizumab. This is to align with other pembrolizumab protocols. • Added exclusion criteria for active tuberculosis in order to align with other pembrolizumab protocols. • Updated text related to pembrolizumab, rescue medications, dose adjustment, overdose, and supportive care guidelines to align with other pembrolizumab protocols. • Updated pregnancy and lactation reporting language to align with other talimogene laherparepvec and pembrolizumab protocols. • Updated language to clarify the modified response criteria in the appendices (eg, how to evaluate separated lesions, criteria for confirmation of PD). • Added optional photography substudy Additional errors were identified and rectified in the superseding amendment, and administrative errors were corrected.

05 January 2017	This protocol was amended to: • Update eligibility criteria triggered by recent safety signal – carotid blowout syndrome, and efficacy signal – lack of benefit in primary refractory patients with progressive disease within 3 months of curative intent multimodality therapy. • Remove progression-free survival as a primary endpoint for phase 3 and make it a secondary endpoint, along with Complete Response Rate (CRR). o The decision to forego of PFS as a dual primary endpoint hinged upon a few factors which included: the recent outcome of CHECKMATE 141 which led to approval of nivolumab based upon OS and also the final approval or pembrolizumab which is dependent upon OS from KEYNOTE 040. Considering the fact that OS is a superior outcome measure of a treatment over PFS especially in a poor prognosis disease and that PFS is not always a surrogate for OS, combined with the precedent set by nivolumab approval on OS, we felt that PFS did not have a truly meaningful role in the assessment of the efficacy of TVEC+pembrolizumab in second line head and neck cancer as well as for regulatory purposes. • Add the use of irRECIST investigator assessment for response assessments and remove RECIST 1.1 central review. • Update QOL/PRO wording and elevation of QLQ C30-3L to secondary endpoint from exploratory. • Update statistical methods to justify the endpoint changes and also to introduce OS IA and futility analyses. • To add more detail around go no go decision from Phase 1b to 3. • Add additional pembrolizumab background information. • Add additional talimogene laherparepvec background information. • Update IP discontinuation/withholding rules. • Update radiographic tumor assessments (sites of disease, spiral CT). • Add additional information for archival tumor tissue. • Add additional information for HPV testing. • Update safety reporting information. • Administrative changes and editorial changes for clarification.
25 October 2017	This protocol was amended to: • Add the investigator-assessed RECIST v1.1 secondary tumor response endpoints of objective response rate (ORR) and progress-free survival (PFS) as secondary endpoints and remove CRR per irRECIST as a secondary endpoint. • Replace EQ-5D-3L with EQ-5D-5L to utilize the most recent PRO version. • Revised re-irradiation exclusion criteria. • Replaced modified RECIST v1.1 of 10 maximum lesions with 5 per organ with standard RECIST v1.1 for screening (5 maximum lesions with 2 per organ) to align with the use of standard RECIST v1.1 introduced for key secondary endpoints. • Added RECIST v1.1 assessment in addition to irRECIST assessment for response assessment. • Revised the set of secondary hypotheses to be tested with the Maurer-Bretz procedure to potentially generate more robust efficacy conclusions. Testing of CRR was replaced with ORR. Testing was added for RECIST v1.1 ORR and PFS. The total number of potential hypotheses tested increased from 3 to 5. • The number of events at the OS interim analysis was increased from approximately 255 to 280 to preserve 70% power in the event of a potential treatment lag effect. • Sample size considerations were revised due to the OS interim analysis change and to discuss the power for the revised secondary hypothesis tests. • The OS futility criterion at the interim analysis was changed from a conditional power <10% given a true HR of 0.70 to an observed HR >0.92 considering a potential treatment lag effect. • An audit-based Blind Independent Central Review (BICR) was added to assess the consistency of investigator- and BICR-assessed treatment effects for RECIST v1.1 ORR and PFS. • The definition of the phase 3 primary efficacy and safety analysis sets, primary completion, and end of trial were revised to maintain the study’s statistical considerations. • Updated language on disease related events and reporting procedures per internal Amgen recommendations and to align across program.

11 May 2018	This protocol was amended to: • Add language to clarify long term follow-up for subjects in phase 1b due to decision to not proceed to the phase 3 part of the study. • Remove PK and ADA samples from phase 1b portion of protocol per discussion with FDA, EMA, and PDMA (Merck request). • Update End of Study language to align with most recent Amgen template text and to include the definition of Primary Completion and End of Trial for subjects who completed phase 1b. • Include a follow-up analysis for phase 1b. • Add text providing guidance about latex allergies to exclusion criteria no. 223. • Update serious adverse event reporting procedures to align with current safety language. • Update pembrolizumab safety language regarding pregnancy reporting and breastfeeding. • Update Key Sponsor Contacts. • Make administrative and editorial changes.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported