Clinical trial results:
Phase 2 Study of Talimogene Laherparepvec in Combination With Pembrolizumab in Subjects With Unresectable/Metastatic Stage IIIB-IVM1d Melanoma Who Have Progressed on Prior Anti-PD-1 Based Therapy

Summary

EudraCT number	2019-001906-61
Trial protocol	NL GR PL ES FR GB DE IT
Global end of trial date	26 February 2024

Results information

Result version number	v1 (current)
This version publication date	28 December 2024
First version publication date	28 December 2024

Trial information

Trial identification

Sponsor protocol code	20180115

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04068181
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amgen Inc.
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, United States, CA
Public contact	Study Director, Amgen Inc., +1 8665726436, medinfo@amgen.com
Scientific contact	Study Director, Amgen Inc., +1 8665726436, medinfo@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	26 February 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 February 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the efficacy of talimogene laherparepvec in combination with pembrolizumab as assessed by objective response rate (ORR) in participants with unresectable/metastatic stage IIIB-IVM1d melanoma who have progressed on prior anti-programmed cell death-1 (anti-PD-1) therapy.

Protection of trial subjects:

I agree to comply with the International Council for Harmonisation Tripartite Guideline on Good Clinical Practice, Declaration of Helsinki, and applicable national or regional regulations/guidelines.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 January 2020
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	36 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 15
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Greece: 12
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Poland: 9
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	United States: 14
Country: Number of subjects enrolled	Australia: 13
Worldwide total number of subjects	72
EEA total number of subjects	44

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)	34
From 65 to 84 years	35
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

72 participants were enrolled at 28 centers in Australia, Canada, France, Germany, Greece, Italy, the Netherlands, Poland, Spain and the United States from 22 January 2020 to 26 February 2024.

Pre-assignment

Screening details:

Participants must have received prior anti-programmed cell death protein (anti-PD-1) therapy for at least 2 to 3 consecutive cycles within an 8-week period and have disease progression as defined by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria.

Pre-assignment period milestones

Number of subjects started	72
Number of subjects completed	71

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Withdrawal of consent from study: 1

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1 – Locally Recurrent/Metastatic - Primary Resistance

Arm description:

Included participants who received anti-PD-1 therapy in the locally recurrent/metastatic setting and experienced a best overall response of disease progression or stable disease prior to confirmed disease progression. Participants received talimogene laherparepvec at an initial dose of up to 4.0 mL of 10^6 plaque-forming units (PFU)/mL by intralesional injection into injectable cutaneous, subcutaneous and nodal legions on Day 1. Subsequent doses of up to 4.0 mL of 10^8 PFU/mL were administered every 3 weeks for up to 35 cycles in total. Participants also received pembrolizumab at a dose of 200 mg as an intravenous (IV) infusion every 3 weeks for up to 35 cycles.

Arm type	Experimental
Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	MK-3475
Other name	Keytruda
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

IV infusion.

Investigational medicinal product name	Talimogene laherparepvec
Investigational medicinal product code	AMG 678
Other name	IMLYGIC
Pharmaceutical forms	Solution for injection
Routes of administration	Intralesional use

Dosage and administration details:

Intralesional injection into injectable cutaneous, subcutaneous and nodal legions.

Arm title	Cohort 2 – Locally Recurrent/Metastatic - Acquired Resistance

Arm description:

Included participants who received anti-PD-1 therapy in the locally recurrent/metastatic setting and experienced confirmed disease progression following a complete or partial response on anti-PD-1 therapy. Participants received talimogene laherparepvec at an initial dose of up to 4.0 mL of 10^6 PFU/mL by intralesional injection into injectable cutaneous, subcutaneous and nodal legions on Day 1. Subsequent doses of up to 4.0 mL of 10^8 PFU/mL were administered every 3 weeks for up to 35 cycles in total. Participants also received pembrolizumab at a dose of 200 mg as an IV infusion every 3 weeks for up to 35 cycles.

Arm type	Experimental
Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	MK-3475
Other name	Keytruda
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

IV infusion.

Investigational medicinal product name	Talimogene laherparepvec
Investigational medicinal product code	AMG 678
Other name	IMLYGIC
Pharmaceutical forms	Solution for injection
Routes of administration	Intralesional use

Dosage and administration details:

Intralesional injection into injectable cutaneous, subcutaneous and nodal legions.

Arm title	Cohort 3 – Adjuvant Setting – Disease Free Interval < 6 months

Arm description:

Included participants who received anti-PD-1 therapy in the adjuvant setting and experienced confirmed disease progression following a disease-free interval of < 6 months after starting the adjuvant anti-PD-1 therapy. Participants received talimogene laherparepvec at an initial dose of up to 4.0 mL of 10^6 PFU/mL by intralesional injection into injectable cutaneous, subcutaneous and nodal legions on Day 1. Subsequent doses of up to 4.0 mL of 10^8 PFU/mL were administered every 3 weeks for up to 35 cycles in total. Participants also received pembrolizumab at a dose of 200 mg as an IV infusion every 3 weeks for up to 35 cycles.

Arm type	Experimental
Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	MK-3475
Other name	Keytruda
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

IV infusion.

Investigational medicinal product name	Talimogene laherparepvec
Investigational medicinal product code	AMG 678
Other name	IMLYGIC
Pharmaceutical forms	Solution for injection
Routes of administration	Intralesional use

Dosage and administration details:

Intralesional injection into injectable cutaneous, subcutaneous and nodal legions.

Arm title	Cohort 4 – Adjuvant Setting – Disease Free Interval ≥ 6 months

Arm description:

Included participants who received anti PD-1 therapy in the adjuvant setting and experienced confirmed disease progression following a disease-free interval of ≥ 6 months after starting the adjuvant PD-1 inhibitor. Participants received talimogene laherparepvec at an initial dose of up to 4.0 mL of 10^6 PFU/mL by intralesional injection into injectable cutaneous, subcutaneous and nodal legions on Day 1. Subsequent doses of up to 4.0 mL of 10^8 PFU/mL were administered every 3 weeks for up to 35 cycles in total. Participants also received pembrolizumab at a dose of 200 mg as an IV infusion every 3 weeks

for up to 35 cycles.

Arm type	Experimental
Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	MK-3475
Other name	Keytruda
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

IV infusion.

Investigational medicinal product name	Talimogene laherparepvec
Investigational medicinal product code	AMG 678
Other name	IMLYGIC
Pharmaceutical forms	Solution for injection
Routes of administration	Intralesional use

Dosage and administration details:

Intralesional injection into injectable cutaneous, subcutaneous and nodal legions.

Number of subjects in period 1[1]	Cohort 1 – Locally Recurrent/Metastatic - Primary Resistance	Cohort 2 – Locally Recurrent/Metastatic - Acquired Resistance	Cohort 3 – Adjuvant Setting – Disease Free Interval < 6 months
Started	26	15	15
Completed	6	3	11
Not completed	20	12	4
Adverse event, non-fatal	17	12	4
Withdrawal of consent from study	2	-	-
Lost to follow-up	1	-	-

Number of subjects in period 1[1]	Cohort 4 – Adjuvant Setting – Disease Free Interval ≥ 6 months
Started	15
Completed	8
Not completed	7
Adverse event, non-fatal	7
Withdrawal of consent from study	-
Lost to follow-up	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Inclusive of participants that received talimogene laherparepvec and pembrolizumab only.

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1 – Locally Recurrent/Metastatic - Primary Resistance
Reporting group description:	
Included participants who received anti-PD-1 therapy in the locally recurrent/metastatic setting and experienced a best overall response of disease progression or stable disease prior to confirmed disease progression. Participants received talimogene laherparepvec at an initial dose of up to 4.0 mL of 10^6 plaque-forming units (PFU)/mL by intralesional injection into injectable cutaneous, subcutaneous and nodal legions on Day 1. Subsequent doses of up to 4.0 mL of 10^8 PFU/mL were administered every 3 weeks for up to 35 cycles in total. Participants also received pembrolizumab at a dose of 200 mg as an intravenous (IV) infusion every 3 weeks for up to 35 cycles.	
Reporting group title	Cohort 2 – Locally Recurrent/Metastatic - Acquired Resistance
Reporting group description:	
Included participants who received anti-PD-1 therapy in the locally recurrent/metastatic setting and experienced confirmed disease progression following a complete or partial response on anti-PD-1 therapy. Participants received talimogene laherparepvec at an initial dose of up to 4.0 mL of 10^6 PFU/mL by intralesional injection into injectable cutaneous, subcutaneous and nodal legions on Day 1. Subsequent doses of up to 4.0 mL of 10^8 PFU/mL were administered every 3 weeks for up to 35 cycles in total. Participants also received pembrolizumab at a dose of 200 mg as an IV infusion every 3 weeks for up to 35 cycles.	
Reporting group title	Cohort 3 – Adjuvant Setting – Disease Free Interval < 6 months
Reporting group description:	
Included participants who received anti-PD-1 therapy in the adjuvant setting and experienced confirmed disease progression following a disease-free interval of < 6 months after starting the adjuvant anti-PD-1 therapy. Participants received talimogene laherparepvec at an initial dose of up to 4.0 mL of 10^6 PFU/mL by intralesional injection into injectable cutaneous, subcutaneous and nodal legions on Day 1. Subsequent doses of up to 4.0 mL of 10^8 PFU/mL were administered every 3 weeks for up to 35 cycles in total. Participants also received pembrolizumab at a dose of 200 mg as an IV infusion every 3 weeks for up to 35 cycles.	
Reporting group title	Cohort 4 – Adjuvant Setting – Disease Free Interval ≥ 6 months
Reporting group description:	
Included participants who received anti PD-1 therapy in the adjuvant setting and experienced confirmed disease progression following a disease-free interval of ≥ 6 months after starting the adjuvant PD-1 inhibitor. Participants received talimogene laherparepvec at an initial dose of up to 4.0 mL of 10^6 PFU/mL by intralesional injection into injectable cutaneous, subcutaneous and nodal legions on Day 1. Subsequent doses of up to 4.0 mL of 10^8 PFU/mL were administered every 3 weeks for up to 35 cycles in total. Participants also received pembrolizumab at a dose of 200 mg as an IV infusion every 3 weeks for up to 35 cycles.	

Reporting group values	Cohort 1 – Locally Recurrent/Metastatic - Primary Resistance	Cohort 2 – Locally Recurrent/Metastatic - Acquired Resistance	Cohort 3 – Adjuvant Setting – Disease Free Interval < 6 months
Number of subjects	26	15	15
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	63.2	65.5	59.4
standard deviation	± 14.6	± 13.2	± 13.0
Sex: Female, Male Units: Subjects			
Female	8	8	5

Male	18	7	10

Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	25	14	14
Unknown or Not Reported	1	1	1
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Black (or African American)	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
White	25	14	14
Other	1	1	1

Reporting group values	Cohort 4 – Adjuvant Setting – Disease Free Interval ≥ 6 months	Total	
Number of subjects	15	71	
Age categorical Units: Subjects			

Age Continuous Units: years			
arithmetic mean	63.5		
standard deviation	± 10.3	-	
Sex: Female, Male Units: Subjects			
Female	2	23	
Male	13	48	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	
Not Hispanic or Latino	15	68	
Unknown or Not Reported	0	3	
Race Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Black (or African American)	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
White	15	68	
Other	0	3	

End points

End points reporting groups

Reporting group title	Cohort 1 – Locally Recurrent/Metastatic - Primary Resistance

Reporting group description:

Included participants who received anti-PD-1 therapy in the locally recurrent/metastatic setting and experienced a best overall response of disease progression or stable disease prior to confirmed disease progression. Participants received talimogene laherparepvec at an initial dose of up to 4.0 mL of 10^6 plaque-forming units (PFU)/mL by intralesional injection into injectable cutaneous, subcutaneous and nodal legions on Day 1. Subsequent doses of up to 4.0 mL of 10^8 PFU/mL were administered every 3 weeks for up to 35 cycles in total. Participants also received pembrolizumab at a dose of 200 mg as an intravenous (IV) infusion every 3 weeks for up to 35 cycles.

Reporting group title	Cohort 2 – Locally Recurrent/Metastatic - Acquired Resistance

Reporting group description:

Included participants who received anti-PD-1 therapy in the locally recurrent/metastatic setting and experienced confirmed disease progression following a complete or partial response on anti-PD-1 therapy. Participants received talimogene laherparepvec at an initial dose of up to 4.0 mL of 10^6 PFU/mL by intralesional injection into injectable cutaneous, subcutaneous and nodal legions on Day 1. Subsequent doses of up to 4.0 mL of 10^8 PFU/mL were administered every 3 weeks for up to 35 cycles in total. Participants also received pembrolizumab at a dose of 200 mg as an IV infusion every 3 weeks for up to 35 cycles.

Reporting group title	Cohort 3 – Adjuvant Setting – Disease Free Interval < 6 months

Reporting group description:

Included participants who received anti-PD-1 therapy in the adjuvant setting and experienced confirmed disease progression following a disease-free interval of < 6 months after starting the adjuvant anti-PD-1 therapy. Participants received talimogene laherparepvec at an initial dose of up to 4.0 mL of 10^6 PFU/mL by intralesional injection into injectable cutaneous, subcutaneous and nodal legions on Day 1. Subsequent doses of up to 4.0 mL of 10^8 PFU/mL were administered every 3 weeks for up to 35 cycles in total. Participants also received pembrolizumab at a dose of 200 mg as an IV infusion every 3 weeks for up to 35 cycles.

Reporting group title	Cohort 4 – Adjuvant Setting – Disease Free Interval ≥ 6 months

Reporting group description:

Included participants who received anti PD-1 therapy in the adjuvant setting and experienced confirmed disease progression following a disease-free interval of ≥ 6 months after starting the adjuvant PD-1 inhibitor. Participants received talimogene laherparepvec at an initial dose of up to 4.0 mL of 10^6 PFU/mL by intralesional injection into injectable cutaneous, subcutaneous and nodal legions on Day 1. Subsequent doses of up to 4.0 mL of 10^8 PFU/mL were administered every 3 weeks for up to 35 cycles in total. Participants also received pembrolizumab at a dose of 200 mg as an IV infusion every 3 weeks for up to 35 cycles.

Primary: ORR per modified RECIST v1.1

End point title	ORR per modified RECIST v1.1[1]

End point description:

ORR was defined as the incidence of a best overall response (BOR) of complete response (CR) or partial response (PR) per modified RECIST v1.1:

- CR: Disappearance of all target and non-target lesions. Any pathological lymph nodes (whether target or non-target) must have had a reduction in short axis to < 10 mm. All lymph nodes must have been non-pathological in size (< 10mm short axis).
- PR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Non-CR/Non-progressive disease (PD): Persistence of 1 or more non-target lesion(s).

Full Analysis Set: Includes all enrolled participants who have received at least 1 dose of talimogene laherparepvec and 1 dose of pembrolizumab in combination.

End point type	Primary

End point timeframe:

Every 12 weeks. Maximum overall time on-study (treatment + follow up) was 46.23 months

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: No additional statistical analysis were pre-specified for this endpoint.

End point values	Cohort 1 – Locally Recurrent/Metastatic - Primary Resistance	Cohort 2 – Locally Recurrent/Metastatic - Acquired Resistance	Cohort 3 – Adjuvant Setting – Disease Free Interval < 6 months	Cohort 4 – Adjuvant Setting – Disease Free Interval ≥ 6 months
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	15	15	15
Units: Percentage of Participants				
number (confidence interval 95%)	3.8 (0.10 to 19.64)	6.7 (0.17 to 31.95)	40.0 (16.34 to 67.71)	46.7 (21.27 to 73.41)

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Response Rate (CRR) per Modified RECIST v1.1

End point title	Complete Response Rate (CRR) per Modified RECIST v1.1

End point description:

CRR was defined as the incidence of a BOR of CR per modified RECIST v1.1:

- CR: Disappearance of all target and non-target lesions. Any pathological lymph nodes (whether target or non-target) must have had a reduction in short axis to < 10 mm. All lymph nodes must have been non-pathological in size (< 10mm short axis).

Confirmation of CR was not required per modified RECIST v1.1.

Values of "-99999" and "99999" represent an N/A value.

Full Analysis Set: Includes all enrolled participants who have received at least 1 dose of talimogene laherparepvec and 1 dose of pembrolizumab in combination.

End point type	Secondary

End point timeframe:

Every 12 weeks. Maximum overall time on-study (treatment + follow up) was 46.23 months

End point values	Cohort 1 – Locally Recurrent/Metastatic - Primary Resistance	Cohort 2 – Locally Recurrent/Metastatic - Acquired Resistance	Cohort 3 – Adjuvant Setting – Disease Free Interval < 6 months	Cohort 4 – Adjuvant Setting – Disease Free Interval ≥ 6 months
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	15	15	15
Units: Percentage of Participants				
number (confidence interval 95%)	0 (-99999 to 99999)	0 (-99999 to 99999)	20.0 (4.33 to 48.09)	20.0 (4.33 to 48.09)

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Response Rate (iCRR) per Modified Immune-related Response Criteria (irRC) RECIST v1.1

End point title	Complete Response Rate (iCRR) per Modified Immune-related Response Criteria (irRC) RECIST v1.1

End point description:

iCRR was defined as the incidence of a best overall response (iBOR) of a complete response (iCR) per modified irRC-RECIST:

- iCR: Disappearance of all lesions (whether measurable or not and whether baseline or new). Any pathological lymph nodes (whether target or nontarget) must have had a reduction in short axis to < 10 mm.

Confirmation of iCR was required per modified irRC-RECIST.

Values of "-99999" and "99999" represent an N/A value.

Full Analysis Set: Includes all enrolled participants who have received at least 1 dose of talimogene laherparepvec and 1 dose of pembrolizumab in combination.

End point type	Secondary

End point timeframe:

Every 12 weeks. Maximum overall time on-study (treatment + follow up) was 46.23 months

End point values	Cohort 1 – Locally Recurrent/Metastatic - Primary Resistance	Cohort 2 – Locally Recurrent/Metastatic - Acquired Resistance	Cohort 3 – Adjuvant Setting – Disease Free Interval < 6 months	Cohort 4 – Adjuvant Setting – Disease Free Interval ≥ 6 months
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	15	15	15
Units: Percentage of Participants				
number (confidence interval 95%)	0 (-99999 to 99999)	0 (-99999 to 99999)	26.7 (7.79 to 55.10)	20.0 (4.33 to 48.09)

Statistical analyses

No statistical analyses for this end point

Secondary: BOR per Modified RECIST v1.1

End point title	BOR per Modified RECIST v1.1

End point description:

BOR was the best overall visit response up to & including the first overall visit response of PD:

-CR: Disappearance of all target & non-target lesions. Any pathological lymph nodes must have had a reduction in short axis to <10 mm. All lymph nodes must have been non-pathological in size.
-PR: ≥30% decrease in the sum of diameters of target lesions.
-Stable disease (SD): Neither sufficient shrinkage to qualify for PR/CR nor sufficient increase to qualify for PD.
-PD: ≥20% increase in the sum of diameters of target lesions and an increase of ≥5mm. Progression of existing non-target lesions.
-Unable to evaluate (UE): Any lesion present at baseline which was not assessed or unable to be evaluated leading to an inability to determine the status of that particular tumor.
-Non-CR/Non-PD: Persistence of 1+ non-target lesion(s). Non-CR/non-PD was relevant to participants who did not have measurable disease at baseline.

Confirmation of CR, PR & PD were not required per modified RECIST 1.1.

End point type	Secondary

End point timeframe:

Every 12 weeks. Maximum overall time on-study (treatment + follow up) was 46.23 months

End point values	Cohort 1 – Locally Recurrent/Metastatic - Primary Resistance	Cohort 2 – Locally Recurrent/Metastatic - Acquired Resistance	Cohort 3 – Adjuvant Setting – Disease Free Interval < 6 months	Cohort 4 – Adjuvant Setting – Disease Free Interval ≥ 6 months
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26[2]	15[3]	15[4]	15[5]
Units: Participants				
CR	0	0	3	3
PR	1	1	3	4
SD	7	4	0	6
PD	11	5	9	1
UE	0	1	0	0
Non-CR/Non-PD	1	0	0	0
Not Done	6	4	0	1

Notes:

[2] - Full Analysis Set.

[3] - Full Analysis Set.

[4] - Full Analysis Set.

[5] - Full Analysis Set.

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Response (iBOR) per Modified irRC-RECIST

End point title	Best Overall Response (iBOR) per Modified irRC-RECIST

End point description:

iBOR was defined as the best overall visit response up to and including the first overall visit response of progressive disease (iPD) per modified irRC-RECIST:

- iCR: Disappearance of all lesions (whether measurable or not and whether baseline or new). Any pathological lymph nodes (whether target or nontarget) must have a reduction in short axis to < 10 mm.
- Partial response (iPR): Decrease in tumor burden ≥ 30% relative to baseline.

- Stable disease (iSD): Neither sufficient shrinkage to qualify for iPR or iCR nor sufficient increase to qualify for iPD.
- iPD: Increase in tumor burden ≥ 20% and at least 5 mm absolute increase.
- Unable to evaluate (iUE): Any lesion present at baseline or a new measurable lesion which was not assessed or was unable to be evaluated leading to an inability to determine the status of that particular tumor for that time point.

Confirmation of iCR, iPR and iPD was required per modified irRC-RECIST.

End point type	Secondary

End point timeframe:

Every 12 weeks. Maximum overall time on-study (treatment + follow up) was 46.23 months

End point values	Cohort 1 – Locally Recurrent/Metastatic - Primary Resistance	Cohort 2 – Locally Recurrent/Metastatic - Acquired Resistance	Cohort 3 – Adjuvant Setting – Disease Free Interval < 6 months	Cohort 4 – Adjuvant Setting – Disease Free Interval ≥ 6 months
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26[6]	15[7]	15[8]	15[9]
Units: Participants				
iCR	0	0	4	3
iPR	3	1	7	4
iSD	10	5	0	6
iPD	5	4	1	0
iUE	2	1	2	1
Not Done	6	4	1	1

Notes:

[6] - Full Analysis Set.

[7] - Full Analysis Set.

[8] - Full Analysis Set.

[9] - Full Analysis Set.

Statistical analyses

No statistical analyses for this end point

Secondary: Durable Response Rate (DRR) per Modified RECIST v1.1

End point title	Durable Response Rate (DRR) per Modified RECIST v1.1

End point description:

DRR was defined as the percentage of participants with a CR or PR per modified RECIST v1.1 with a duration of response (DOR) ≥ 6 months. One month was calculated based on 365.25 days per year.

- CR: Disappearance of all target and non-target lesions. Any pathological lymph nodes (whether target or non-target) must have had a reduction in short axis to < 10 mm. All lymph nodes must have been non-pathological in size (< 10mm short axis).
- PR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Confirmation of CR and PR were not required per modified RECIST v1.1.

Full Analysis Set: Includes all enrolled participants who have received at least 1 dose of talimogene laherparepvec and 1 dose of pembrolizumab in combination.

End point type	Secondary

End point timeframe:

Every 12 weeks. Maximum overall time on-study (treatment + follow up) was 46.23 months

End point values	Cohort 1 – Locally Recurrent/Metastatic - Primary Resistance	Cohort 2 – Locally Recurrent/Metastatic - Acquired Resistance	Cohort 3 – Adjuvant Setting – Disease Free Interval < 6 months	Cohort 4 – Adjuvant Setting – Disease Free Interval ≥ 6 months
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	15	15	15
Units: Percentage of Participants				
number (confidence interval 95%)	3.8 (0.10 to 19.64)	6.7 (0.17 to 31.95)	40.0 (16.34 to 67.71)	26.7 (7.79 to 55.10)

Statistical analyses

No statistical analyses for this end point

Secondary: Durable Response Rate (iDRR) per Modified irRC-RECIST

End point title	Durable Response Rate (iDRR) per Modified irRC-RECIST

End point description:

iDRR was defined as the percentage of participants with an iCR or iPR per modified irRC-RECIST with a duration of response (iDOR) ≥ 6 months. One month was calculated based on 365.25 days per year.

- iCR: Disappearance of all lesions (whether measurable or not and whether baseline or new). Any pathological lymph nodes (whether target or nontarget) must have a reduction in short axis to < 10 mm.
- iPR: Decrease in tumor burden ≥ 30% relative to baseline.

Confirmation of iCR and iPR were required per modified irRC-RECIST.

Full Analysis Set: Includes all enrolled participants who have received at least 1 dose of talimogene laherparepvec and 1 dose of pembrolizumab in combination.

End point type	Secondary

End point timeframe:

Every 12 weeks. Maximum overall time on-study (treatment + follow up) was 46.23 months

End point values	Cohort 1 – Locally Recurrent/Metastatic - Primary Resistance	Cohort 2 – Locally Recurrent/Metastatic - Acquired Resistance	Cohort 3 – Adjuvant Setting – Disease Free Interval < 6 months	Cohort 4 – Adjuvant Setting – Disease Free Interval ≥ 6 months
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	15	15	15
Units: Percentage of Participants				
number (confidence interval 95%)	11.5 (2.45 to 30.15)	6.7 (0.17 to 31.95)	73.3 (44.90 to 92.21)	40.0 (16.34 to 67.71)

Statistical analyses

No statistical analyses for this end point

Secondary: DOR per Modified RECIST v1.1

End point title	DOR per Modified RECIST v1.1

End point description:

DOR was defined as the time from the date of an initial response of CR or PR to the earlier of PD/death. Participants who had not ended their response at the time of analysis were censored at their last evaluable tumor assessment date.

-CR:Disappearance of all target & non-target lesions. All lymph nodes must have a reduction in short axis to <10 mm. Any pathological lymph nodes must have had a reduction in short axis to <10 mm. All lymph nodes must have been non-pathological in size (<10mm short axis).
-PR:At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
-PD:At least a 20% increase in the sum of diameters of target lesions. The sum must also demonstrate an increase of at least 5mm. Unequivocal progression of existing non-target lesions.

Confirmation of CR, PR and PD were not required per modified RECIST v1.1.

Values of "-99999" and "99999" represent an N/A value.

End point type	Secondary

End point timeframe:

Every 12 weeks. Maximum overall time on-study (treatment + follow up) was 46.23 months

End point values	Cohort 1 – Locally Recurrent/Metastatic - Primary Resistance	Cohort 2 – Locally Recurrent/Metastatic - Acquired Resistance	Cohort 3 – Adjuvant Setting – Disease Free Interval < 6 months	Cohort 4 – Adjuvant Setting – Disease Free Interval ≥ 6 months
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1[10]	1[11]	6[12]	7[13]
Units: Months				
median (confidence interval 95%)	22.768 (-99999 to 99999)	7.655 (-99999 to 99999)	99999 (19.351 to 99999)	13.700 (5.520 to 99999)

Notes:

[10] - Full Analysis Set. Only participants who had an initial response of CR or PR were included.

[11] - Full Analysis Set. Only participants who had an initial response of CR or PR were included.

[12] - Full Analysis Set. Only participants who had an initial response of CR or PR were included.

[13] - Full Analysis Set. Only participants who had an initial response of CR or PR were included.

Statistical analyses

No statistical analyses for this end point

Secondary: iDOR per Modified irRC-RECIST

End point title	iDOR per Modified irRC-RECIST

End point description:

iDOR was defined as the time from the date of an initial response that is subsequently confirmed to the earlier of iPD per modified irRC-RECIST.
Participants who had not ended their response at the time of analysis were censored at their last evaluable tumor assessment date.

- iCR: Disappearance of all target and non-target lesions. All lymph nodes must have a reduction in short axis to < 10 mm.
- iPR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- iPD: At least a 20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm. Unequivocal progression of existing non-target lesions.

Values of "-99999" and "99999" represent an N/A value.

End point type	Secondary

End point timeframe:

Every 12 weeks. Maximum overall time on-study (treatment + follow up) was 46.23 months

End point values	Cohort 1 – Locally Recurrent/Metastatic - Primary Resistance	Cohort 2 – Locally Recurrent/Metastatic - Acquired Resistance	Cohort 3 – Adjuvant Setting – Disease Free Interval < 6 months	Cohort 4 – Adjuvant Setting – Disease Free Interval ≥ 6 months
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3[14]	1[15]	11[16]	7[17]
Units: Months				
median (confidence interval 95%)	99999 (22.768 to 99999)	7.655 (-99999 to 99999)	99999 (-99999 to 99999)	99999 (11.302 to 99999)

Notes:

[14] - Full Analysis Set. Only participants who had an initial response of iCR or iPR were included.

[15] - Full Analysis Set. Only participants who had an initial response of iCR or iPR were included.

[16] - Full Analysis Set. Only participants who had an initial response of iCR or iPR were included.

[17] - Full Analysis Set. Only participants who had an initial response of iCR or iPR were included.

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR) per Modified RECIST v1.1

End point title	Disease Control Rate (DCR) per Modified RECIST v1.1

End point description:

DCR per modified RECIST v1.1 was defined as the incidence of a BOR of CR, PR or SD.

- CR: Disappearance of all target and non-target lesions. Any pathological lymph nodes (whether target or non-target) must have had a reduction in short axis to < 10 mm. All lymph nodes must have been non-pathological in size (< 10mm short axis
- PR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- SD: Neither sufficient shrinkage to qualify for PR or CR nor sufficient increase to qualify for PD.

Confirmation of CR and PR were not required per modified RECIST v1.1.

Full Analysis Set: Includes all enrolled participants who have received at least 1 dose of talimogene

laherparepvec and 1 dose of pembrolizumab in combination.

End point type	Secondary

End point timeframe:

Every 12 weeks. Maximum overall time on-study (treatment + follow up) was 46.23 months

End point values	Cohort 1 – Locally Recurrent/Metastatic - Primary Resistance	Cohort 2 – Locally Recurrent/Metastatic - Acquired Resistance	Cohort 3 – Adjuvant Setting – Disease Free Interval < 6 months	Cohort 4 – Adjuvant Setting – Disease Free Interval ≥ 6 months
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	15	15	15
Units: Percentage of Participants				
number (confidence interval 95%)	30.8 (14.33 to 51.79)	33.3 (11.82 to 61.62)	40.0 (16.34 to 67.71)	86.7 (59.54 to 98.34)

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (iORR) per Modified irRC-RECIST

End point title	Objective Response Rate (iORR) per Modified irRC-RECIST

End point description:

iORR was defined as the incidence of an iBOR of iCR or iPR per modified irRC-RECIST

- iCR: Disappearance of all lesions (whether measurable or not and whether baseline or new). Any pathological lymph nodes (whether target or nontarget) must have a reduction in short axis to < 10 mm.
- iPR: Decrease in tumor burden ≥ 30% relative to baseline.

Confirmation of iCR and iPR were required per modified irRC-RECIST.

Full Analysis Set: Includes all enrolled participants who have received at least 1 dose of talimogene laherparepvec and 1 dose of pembrolizumab in combination.

End point type	Secondary

End point timeframe:

Every 12 weeks. Maximum overall time on-study (treatment + follow up) was 46.23 months

End point values	Cohort 1 – Locally Recurrent/Metastatic - Primary Resistance	Cohort 2 – Locally Recurrent/Metastatic - Acquired Resistance	Cohort 3 – Adjuvant Setting – Disease Free Interval < 6 months	Cohort 4 – Adjuvant Setting – Disease Free Interval ≥ 6 months
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	15	15	15
Units: Percentage of Participants				
number (confidence interval 95%)	11.5 (2.45 to 30.15)	6.7 (0.17 to 31.95)	73.3 (44.90 to 92.21)	46.7 (21.27 to 73.41)

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (iDCR) per Modified irRC-RECIST

End point title	Disease Control Rate (iDCR) per Modified irRC-RECIST

End point description:

iDCR per modified irRC-RECIST was defined as the incidence of an iBOR of iCR, iPR or iSD.

- iCR: Disappearance of all target and non-target lesions. All lymph nodes must have a reduction in short axis to < 10 mm.
- iPR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- iSD: Neither sufficient shrinkage to qualify for iPR or iCR nor sufficient increase to qualify for iPD.

Confirmation of iCR and iPR were required per modified irRC-RECIST.

Full Analysis Set: Includes all enrolled participants who have received at least 1 dose of talimogene laherparepvec and 1 dose of pembrolizumab in combination.

End point type	Secondary

End point timeframe:

Every 12 weeks. Maximum overall time on-study (treatment + follow up) was 46.23 months

End point values	Cohort 1 – Locally Recurrent/Metastatic - Primary Resistance	Cohort 2 – Locally Recurrent/Metastatic - Acquired Resistance	Cohort 3 – Adjuvant Setting – Disease Free Interval < 6 months	Cohort 4 – Adjuvant Setting – Disease Free Interval ≥ 6 months
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	15	15	15
Units: Percentage of Participants				
number (confidence interval 95%)	50.0 (29.93 to 70.07)	40.0 (16.34 to 67.71)	73.3 (44.90 to 92.21)	86.7 (59.54 to 98.34)

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (iPFS) per Modified irRC-RECIST

End point title	Progression Free Survival (iPFS) per Modified irRC-RECIST

End point description:

iPFS per modified irRC-RECIST was defined as the interval from first dose to the earlier event of iPD or death from any cause. Participants without an event were censored at their last evaluable post-baseline tumor assessment if available, otherwise were censored on study Day 1. One month was calculated

based on 365.25 days per year.

- iPD: Increase in tumor burden ≥ 20% and at least 5 mm absolute increase.

Values of "99999" represent an N/A value.

Full Analysis Set: Includes all enrolled participants who have received at least 1 dose of talimogene laherparepvec and 1 dose of pembrolizumab in combination.

End point type	Secondary

End point timeframe:

Every 12 weeks. Maximum overall time on-study (treatment + follow up) was 46.23 months

End point values	Cohort 1 – Locally Recurrent/Metastatic - Primary Resistance	Cohort 2 – Locally Recurrent/Metastatic - Acquired Resistance	Cohort 3 – Adjuvant Setting – Disease Free Interval < 6 months	Cohort 4 – Adjuvant Setting – Disease Free Interval ≥ 6 months
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	15	15	15
Units: Months				
median (confidence interval 95%)	6.899 (2.793 to 25.232)	8.214 (2.694 to 15.014)	99999 (2.694 to 99999)	25.955 (16.756 to 99999)

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) per Modified RECIST v1.1

End point title	Progression Free Survival (PFS) per Modified RECIST v1.1

End point description:

PFS per modified RECIST 1.1 was defined as the interval from first dose to the earlier event of PD or death from any cause. Participants without an event were censored at their last evaluable post-baseline tumor assessment if available, otherwise were censored on study Day 1. One month was calculated based on 365.25 days per year.

- PD: At least a 20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm. Unequivocal progression of existing non-target lesions.

Full Analysis Set: Includes all enrolled participants who have received at least 1 dose of talimogene laherparepvec and 1 dose of pembrolizumab in combination.

End point type	Secondary

End point timeframe:

Every 12 weeks. Maximum overall time on-study (treatment + follow up) was 46.23 months

End point values	Cohort 1 – Locally Recurrent/Metastatic - Primary Resistance	Cohort 2 – Locally Recurrent/Metastatic - Acquired Resistance	Cohort 3 – Adjuvant Setting – Disease Free Interval < 6 months	Cohort 4 – Adjuvant Setting – Disease Free Interval ≥ 6 months
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	15	15	15
Units: Months				
median (confidence interval 95%)	3.614 (2.793 to 5.520)	4.830 (2.431 to 13.207)	2.793 (2.661 to 27.433)	13.897 (5.552 to 19.318)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Experienced a Treatment-emergent Adverse Event (TEAE)

End point title	Number of Participants Who Experienced a Treatment-emergent Adverse Event (TEAE)

End point description:

Evaluation of TEAEs included the number of participants with at least 1:
- TEAE
- Treatment-related TEAE
- Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3 TEAE
- Treatment-related CTCAE grade ≥ 3 TEAE
- Serious TEAE
- Serious treatment-related TEAE
- Fatal TEAE
- Fatal treatment-related TEAE
- TEAE of interest

Serious TEAEs were collected up to 90 days post-last dose of treatment. Non-serious TEAEs were collected up to 30 days post-last dose of treatment.

A CTCAE grade ≥ 3 was determined using the CTCAE grading systems based on CTCAE version 5.0 per the below definitions:
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activities of daily living.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to TEAE.

Abnormal laboratory tests were also recorded as TEAEs.

End point type	Secondary

End point timeframe:

Serious TEAEs were collected up to 90 days post-last dose of treatment. Non-serious TEAEs were collected up to 30 days post-last dose of treatment. The maximum duration of treatment exposure was 105.9 weeks.

End point values	Cohort 1 – Locally Recurrent/Metastatic - Primary Resistance	Cohort 2 – Locally Recurrent/Metastatic - Acquired Resistance	Cohort 3 – Adjuvant Setting – Disease Free Interval < 6 months	Cohort 4 – Adjuvant Setting – Disease Free Interval ≥ 6 months
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26[18]	15[19]	15[20]	15[21]
Units: Participants				
TEAEs	24	15	15	14
Treatment-related TEAEs	17	10	14	13
CTCAE Grade ≥ 3 TEAEs	11	8	4	8
CTCAE Grade ≥ 3 Treatment-related TEAEs	2	3	0	6
Serious TEAEs	12	7	4	7
Serious Treatment-related TEAEs	1	2	0	3
Fatal TEAEs	5	3	1	3
Fatal Treatment-related TEAEs	0	0	0	1
TEAEs of Interest	21	14	15	14

Notes:

[18] - Safety Analysis Set: All enrolled participants who received at least 1 dose of study treatment.

[19] - Safety Analysis Set: All enrolled participants who received at least 1 dose of study treatment.

[20] - Safety Analysis Set: All enrolled participants who received at least 1 dose of study treatment.

[21] - Safety Analysis Set: All enrolled participants who received at least 1 dose of study treatment.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the interval from first dose to death from any cause. Participants without an event were censored at the last date known to be alive. One month was calculated based on 365.25 days per year.

Values of "99999" represent an N/A value.

Full Analysis Set: Includes all enrolled participants who have received at least 1 dose of talimogene laherparepvec and 1 dose of pembrolizumab in combination.

End point type	Secondary

End point timeframe:

Every 12 weeks. Maximum overall time on-study (treatment + follow up) was 46.23 months

End point values	Cohort 1 – Locally Recurrent/Metastatic - Primary Resistance	Cohort 2 – Locally Recurrent/Metastatic - Acquired Resistance	Cohort 3 – Adjuvant Setting – Disease Free Interval < 6 months	Cohort 4 – Adjuvant Setting – Disease Free Interval ≥ 6 months
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	15	15	15
Units: Months				
median (confidence interval 95%)	24.608 (6.538	15.014 (2.760	99999 (8.575	99999 (20.370

to 42.086)	to 38.374)	to 99999)	to 99999)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Subsequent Anti-cancer Therapy

End point title	Time to First Subsequent Anti-cancer Therapy

End point description:

Time to first subsequent anti-cancer therapy was defined as the time from enrollment to the start of subsequent anticancer therapy. Participants who did not start subsequent anticancer therapy were censored as the last known to be alive date. One month was calculated based on 365.25 days per year.

Values of "99999" represent an N/A value.

Full Analysis Set: Includes all enrolled participants who have received at least 1 dose of talimogene laherparepvec and 1 dose of pembrolizumab in combination.

End point type	Secondary

End point timeframe:

Every 12 weeks. Maximum overall time on-study (treatment + follow up) was 46.23 months

End point values	Cohort 1 – Locally Recurrent/Metastatic - Primary Resistance	Cohort 2 – Locally Recurrent/Metastatic - Acquired Resistance	Cohort 3 – Adjuvant Setting – Disease Free Interval < 6 months	Cohort 4 – Adjuvant Setting – Disease Free Interval ≥ 6 months
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	15	15	15
Units: Months				
median (confidence interval 95%)	11.466 (6.209 to 38.111)	7.852 (2.793 to 99999)	99999 (25.758 to 99999)	23.097 (11.532 to 99999)

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

Serious TEAEs were collected up to 90 days post-last dose of treatment. Non-serious TEAEs were collected up to 30 days post-last dose of treatment. The maximum duration of treatment exposure was 105.9 weeks .

Adverse event reporting additional description:

All-cause mortality was collected for all enrolled participants. Serious TEAEs and non-serious TEAEs were collected for the safety analysis set which included all enrolled participants who received at least 1 dose of talimogene laherparepvec or pembrolizumab.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	Cohort 1 – Locally Recurrent/Metastatic - Primary Resistance

Reporting group description:

Included participants who received anti-PD-1 therapy in the locally recurrent/metastatic setting and experienced a best overall response of disease progression or stable disease prior to confirmed disease progression. Participants received talimogene laherparepvec at an initial dose of up to 4.0 mL of 10^6 PFU/mL by intralesional injection into injectable cutaneous, subcutaneous and nodal legions on Day 1. Subsequent doses of up to 4.0 mL of 10^8 PFU/mL were administered every 3 weeks for up to 35 cycles in total. Participants also received pembrolizumab at a dose of 200 mg as an IV infusion every 3 weeks for up to 35 cycles.

Reporting group title	Cohort 4 – Adjuvant Setting – Disease Free Interval ≥ 6 months

Reporting group description:

Included participants who received anti PD-1 therapy in the adjuvant setting and experienced confirmed disease progression following a disease-free interval of ≥ 6 months after starting the adjuvant PD-1 inhibitor. Participants received talimogene laherparepvec at an initial dose of up to 4.0 mL of 10^6 PFU/mL by intralesional injection into injectable cutaneous, subcutaneous and nodal legions on Day 1. Subsequent doses of up to 4.0 mL of 10^8 PFU/mL were administered every 3 weeks for up to 35 cycles in total. Participants also received pembrolizumab at a dose of 200 mg as an IV infusion every 3 weeks for up to 35 cycles.

Reporting group title	Cohort 3 – Adjuvant Setting – Disease Free Interval < 6 months

Reporting group description:

Included participants who received anti-PD-1 therapy in the adjuvant setting and experienced confirmed disease progression following a disease-free interval of < 6 months after starting the adjuvant anti-PD-1 therapy. Participants received talimogene laherparepvec at an initial dose of up to 4.0 mL of 10^6 PFU/mL by intralesional injection into injectable cutaneous, subcutaneous and nodal legions on Day 1. Subsequent doses of up to 4.0 mL of 10^8 PFU/mL were administered every 3 weeks for up to 35 cycles in total. Participants also received pembrolizumab at a dose of 200 mg as an IV infusion every 3 weeks for up to 35 cycles.

Reporting group title	Cohort 2 – Locally Recurrent/Metastatic - Acquired Resistance

Reporting group description:

Included participants who received anti-PD-1 therapy in the locally recurrent/metastatic setting and experienced confirmed disease progression following a complete or partial response on anti-PD-1 therapy. Participants received talimogene laherparepvec at an initial dose of up to 4.0 mL of 10^6 PFU/mL by intralesional injection into injectable cutaneous, subcutaneous and nodal legions on Day 1. Subsequent doses of up to 4.0 mL of 10^8 PFU/mL were administered every 3 weeks for up to 35 cycles in total. Participants also received pembrolizumab at a dose of 200 mg as an IV infusion every 3 weeks for up to 35 cycles.

Serious adverse events	Cohort 1 – Locally Recurrent/Metastatic - Primary Resistance	Cohort 4 – Adjuvant Setting – Disease Free Interval ≥ 6 months	Cohort 3 – Adjuvant Setting – Disease Free Interval < 6 months
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 26 (46.15%)	7 / 15 (46.67%)	4 / 15 (26.67%)
number of deaths (all causes)	17	7	4
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma			
subjects affected / exposed	2 / 26 (7.69%)	1 / 15 (6.67%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Cancer pain			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain neoplasm			
subjects affected / exposed	1 / 26 (3.85%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastatic malignant melanoma			

subjects affected / exposed	3 / 26 (11.54%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 0
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	2 / 26 (7.69%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 26 (0.00%)	2 / 15 (13.33%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 2	0 / 0
Pyrexia			
subjects affected / exposed	1 / 26 (3.85%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	1 / 26 (3.85%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 26 (3.85%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Subdural haematoma			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain oedema			
subjects affected / exposed	1 / 26 (3.85%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	1 / 26 (3.85%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	1 / 26 (3.85%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Intussusception			
subjects affected / exposed	1 / 26 (3.85%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Liver injury			
subjects affected / exposed	1 / 26 (3.85%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Purpura			
subjects affected / exposed	1 / 26 (3.85%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Renal and urinary disorders			
Renal disorder			
subjects affected / exposed	1 / 26 (3.85%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Adrenocortical insufficiency acute			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophysitis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Polymyalgia rheumatica			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	1 / 26 (3.85%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			

subjects affected / exposed	1 / 26 (3.85%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 26 (3.85%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	1 / 26 (3.85%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	1 / 26 (3.85%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort 2 – Locally		

	Recurrent/Metastatic - Acquired Resistance		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 15 (46.67%)		
number of deaths (all causes)	12		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Basal cell carcinoma			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Malignant melanoma			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cancer pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Brain neoplasm			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metastatic malignant melanoma			

subjects affected / exposed	2 / 15 (13.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Chronic obstructive pulmonary disease				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Subdural haematoma				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fall				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Bradycardia				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure congestive				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Dizziness				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Brain oedema				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				

subjects affected / exposed	0 / 15 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Intussusception			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Liver injury			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholecystitis			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Purpura			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Renal and urinary disorders			
Renal disorder			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Adrenocortical insufficiency acute			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypophysitis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Polymyalgia rheumatica			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cellulitis			

subjects affected / exposed	0 / 15 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia bacterial			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Sepsis			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Cohort 1 – Locally Recurrent/Metastatic - Primary Resistance	Cohort 4 – Adjuvant Setting – Disease Free Interval ≥ 6 months	Cohort 3 – Adjuvant Setting – Disease Free Interval < 6 months
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 26 (76.92%)	14 / 15 (93.33%)	15 / 15 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 26 (3.85%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Seborrhoeic keratosis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Tumour fistulisation			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Benign salivary gland neoplasm			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Tumour pain			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	0	2	0
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 26 (3.85%)	2 / 15 (13.33%)	0 / 15 (0.00%)
occurrences (all)	1	2	0
Hypertension			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Surgical and medical procedures			
Skin neoplasm excision			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			

Chest pain			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Chest discomfort			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Axillary pain			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Asthenia			
subjects affected / exposed	3 / 26 (11.54%)	2 / 15 (13.33%)	2 / 15 (13.33%)
occurrences (all)	4	2	6
Chills			
subjects affected / exposed	6 / 26 (23.08%)	2 / 15 (13.33%)	2 / 15 (13.33%)
occurrences (all)	12	21	2
Fatigue			
subjects affected / exposed	4 / 26 (15.38%)	5 / 15 (33.33%)	6 / 15 (40.00%)
occurrences (all)	5	5	6
Hyperthermia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	5
Influenza like illness			
subjects affected / exposed	2 / 26 (7.69%)	2 / 15 (13.33%)	7 / 15 (46.67%)
occurrences (all)	4	21	26
Injection site extravasation			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Injection site haemorrhage			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Injection site inflammation			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	7 / 26 (26.92%)	7 / 15 (46.67%)	5 / 15 (33.33%)
occurrences (all)	12	10	8

Peripheral swelling			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Pain			
subjects affected / exposed	2 / 26 (7.69%)	3 / 15 (20.00%)	0 / 15 (0.00%)
occurrences (all)	3	5	0
Injection site reaction			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	3
Injection site paraesthesia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Injection site pain			
subjects affected / exposed	3 / 26 (11.54%)	1 / 15 (6.67%)	4 / 15 (26.67%)
occurrences (all)	3	1	5
Injection site oedema			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Face oedema			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Xerosis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Oedema peripheral			
subjects affected / exposed	1 / 26 (3.85%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Immune system disorders			
Contrast media allergy			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Sarcoidosis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Seasonal allergy			

subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Cervical dysplasia			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Penile dermatitis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	0	2	0
Cough			
subjects affected / exposed	0 / 26 (0.00%)	2 / 15 (13.33%)	3 / 15 (20.00%)
occurrences (all)	0	2	4
Dyspnoea			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Dyspnoea exertional			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Laryngeal inflammation			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Oropharyngeal pain			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Pleural effusion			
subjects affected / exposed	1 / 26 (3.85%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Depressed mood			

subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Depression			
subjects affected / exposed	1 / 26 (3.85%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Sleep disorder			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	2
Insomnia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Anxiety			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 26 (3.85%)	1 / 15 (6.67%)	1 / 15 (6.67%)
occurrences (all)	2	2	1
Lipase increased			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Blood creatinine increased			
subjects affected / exposed	2 / 26 (7.69%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	2	2	0
Blood pressure increased			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Blood thyroid stimulating hormone increased			
subjects affected / exposed	1 / 26 (3.85%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Body temperature increased			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Gamma-glutamyltransferase increased			

subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	2
Alanine aminotransferase increased			
subjects affected / exposed	1 / 26 (3.85%)	2 / 15 (13.33%)	1 / 15 (6.67%)
occurrences (all)	5	4	1
Weight decreased			
subjects affected / exposed	2 / 26 (7.69%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	2	2	0
Transaminases increased			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Lymphocyte count decreased			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	0	4	0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Subdural haematoma			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Limb injury			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	2
Ligament sprain			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Head injury			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Accident at home			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Wound dehiscence			

subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Skin wound			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	2
Skin laceration			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Immunisation reaction			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 26 (3.85%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Paraesthesia			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Migraine			
subjects affected / exposed	1 / 26 (3.85%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Lethargy			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	2
Headache			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	5 / 15 (33.33%)
occurrences (all)	0	1	9
Dizziness			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Sciatica			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0

Blood and lymphatic system disorders			
Anaemia vitamin B12 deficiency			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Eosinophilia			
subjects affected / exposed	1 / 26 (3.85%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	1	12	0
Neutropenia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	4
Anaemia			
subjects affected / exposed	4 / 26 (15.38%)	2 / 15 (13.33%)	1 / 15 (6.67%)
occurrences (all)	4	5	1
Thrombocytopenia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Leukopenia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Dry eye			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Retinal disorder			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Vision blurred			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Xerophthalmia			

subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Conjunctival suffusion			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Abdominal pain			
subjects affected / exposed	1 / 26 (3.85%)	2 / 15 (13.33%)	1 / 15 (6.67%)
occurrences (all)	2	2	1
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Dyspepsia			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Diarrhoea			
subjects affected / exposed	3 / 26 (11.54%)	7 / 15 (46.67%)	2 / 15 (13.33%)
occurrences (all)	3	12	5
Constipation			
subjects affected / exposed	0 / 26 (0.00%)	2 / 15 (13.33%)	0 / 15 (0.00%)
occurrences (all)	0	2	0
Colitis			
subjects affected / exposed	1 / 26 (3.85%)	2 / 15 (13.33%)	2 / 15 (13.33%)
occurrences (all)	2	3	2
Anal haemorrhage			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Abdominal pain upper			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	3
Nausea			
subjects affected / exposed	6 / 26 (23.08%)	3 / 15 (20.00%)	3 / 15 (20.00%)
occurrences (all)	9	3	6

Vomiting			
subjects affected / exposed	4 / 26 (15.38%)	2 / 15 (13.33%)	0 / 15 (0.00%)
occurrences (all)	4	2	0
Toothache			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Stomatitis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Rectal haemorrhage			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Haemorrhoids			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Gastritis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Enteritis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Dysphagia			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Dry mouth			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Change of bowel habit			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	0	2	0
Hepatic cytolysis			

subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Umbilical discharge			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Skin hypopigmentation			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	0	2	0
Skin hyperplasia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Scab			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Rash maculo-papular			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Rash			
subjects affected / exposed	2 / 26 (7.69%)	1 / 15 (6.67%)	4 / 15 (26.67%)
occurrences (all)	3	1	4
Pruritus			
subjects affected / exposed	2 / 26 (7.69%)	2 / 15 (13.33%)	5 / 15 (33.33%)
occurrences (all)	2	2	6
Hair colour changes			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Erythema			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Eczema			
subjects affected / exposed	0 / 26 (0.00%)	2 / 15 (13.33%)	1 / 15 (6.67%)
occurrences (all)	0	2	1
Dry skin			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	2

Dermatitis contact			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Alopecia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	2
Vitiligo			
subjects affected / exposed	2 / 26 (7.69%)	2 / 15 (13.33%)	1 / 15 (6.67%)
occurrences (all)	2	2	1
Skin lesion			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Rash papular			
subjects affected / exposed	0 / 26 (0.00%)	2 / 15 (13.33%)	0 / 15 (0.00%)
occurrences (all)	0	2	0
Rash macular			
subjects affected / exposed	1 / 26 (3.85%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Rash erythematous			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Psoriasis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Lichen planus			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Dermatitis allergic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Skin burning sensation			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Rash pruritic			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	0	1	0

Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Pollakiuria			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Proteinuria			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Urethral dilatation			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 26 (3.85%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Hypophysitis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	0	2	0
Hyperthyroidism			
subjects affected / exposed	1 / 26 (3.85%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Joint effusion			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Compartment syndrome			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Bone pain			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0

Back pain			
subjects affected / exposed	2 / 26 (7.69%)	1 / 15 (6.67%)	4 / 15 (26.67%)
occurrences (all)	2	2	4
Arthritis			
subjects affected / exposed	0 / 26 (0.00%)	3 / 15 (20.00%)	0 / 15 (0.00%)
occurrences (all)	0	3	0
Arthralgia			
subjects affected / exposed	3 / 26 (11.54%)	4 / 15 (26.67%)	2 / 15 (13.33%)
occurrences (all)	3	5	4
Musculoskeletal chest pain			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	1 / 15 (6.67%)
occurrences (all)	0	1	2
Myalgia			
subjects affected / exposed	3 / 26 (11.54%)	0 / 15 (0.00%)	4 / 15 (26.67%)
occurrences (all)	3	0	6
Neck pain			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Pain in extremity			
subjects affected / exposed	4 / 26 (15.38%)	2 / 15 (13.33%)	2 / 15 (13.33%)
occurrences (all)	6	2	2
Rhabdomyolysis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Rheumatic disorder			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Tendonitis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Musculoskeletal stiffness			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Muscle spasms			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0

Joint stiffness			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Infections and infestations			
Skin infection			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Tinea versicolour			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Rhinitis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	2 / 15 (13.33%)
occurrences (all)	0	2	3
Cellulitis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Cellulitis orbital			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Clostridium difficile infection			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Diarrhoea infectious			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Enterocolitis infectious			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Genital herpes simplex			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Herpes simplex			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Herpes simplex reactivation			

subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Herpes zoster			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Oral herpes			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Respiratory tract infection			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Wound infection			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
COVID-19			
subjects affected / exposed	1 / 26 (3.85%)	0 / 15 (0.00%)	2 / 15 (13.33%)
occurrences (all)	1	0	2
Cystitis			
subjects affected / exposed	2 / 26 (7.69%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences (all)	2	0	0
Dermatophytosis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Vaginal infection			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Postoperative wound infection			
subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Fungal skin infection			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Mastoiditis			

subjects affected / exposed	0 / 26 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hypomagnesaemia			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Hypokalaemia			
subjects affected / exposed	2 / 26 (7.69%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	2	1	0
Hypocalcaemia			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Hyperglycaemia			
subjects affected / exposed	2 / 26 (7.69%)	2 / 15 (13.33%)	0 / 15 (0.00%)
occurrences (all)	2	3	0
Gout			
subjects affected / exposed	0 / 26 (0.00%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Decreased appetite			
subjects affected / exposed	3 / 26 (11.54%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	4	1	0
Hypophosphataemia			
subjects affected / exposed	1 / 26 (3.85%)	1 / 15 (6.67%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Hyponatraemia			
subjects affected / exposed	1 / 26 (3.85%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Hyperuricaemia			
subjects affected / exposed	1 / 26 (3.85%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Cohort 2 – Locally Recurrent/Metastatic - Acquired Resistance		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 15 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Cancer pain subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 2		
Seborrhoeic keratosis subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Tumour fistulisation subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Benign salivary gland neoplasm subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Tumour pain subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Vascular disorders			
Hypotension subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Hypertension subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Surgical and medical procedures			
Skin neoplasm excision subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
General disorders and administration site conditions			
Chest pain subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Chest discomfort subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Axillary pain subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		

Asthenia				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	2			
Chills				
subjects affected / exposed	2 / 15 (13.33%)			
occurrences (all)	3			
Fatigue				
subjects affected / exposed	5 / 15 (33.33%)			
occurrences (all)	5			
Hyperthermia				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Influenza like illness				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Injection site extravasation				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Injection site haemorrhage				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Injection site inflammation				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Pyrexia				
subjects affected / exposed	6 / 15 (40.00%)			
occurrences (all)	12			
Peripheral swelling				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Pain				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Injection site reaction				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			

Injection site paraesthesia subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Injection site pain subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 2		
Injection site oedema subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Face oedema subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Xerosis subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Oedema peripheral subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Immune system disorders Contrast media allergy subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Sarcoidosis subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Seasonal allergy subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Reproductive system and breast disorders Cervical dysplasia subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Penile dermatitis subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders			

Rhinorrhoea subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0			
Cough subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0			
Dyspnoea subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0			
Dyspnoea exertional subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1			
Laryngeal inflammation subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0			
Oropharyngeal pain subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1			
Pleural effusion subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 3			
Psychiatric disorders Delirium subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 2			
Depressed mood subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0			
Depression subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0			
Sleep disorder subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0			
Insomnia				

subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Anxiety			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Lipase increased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	4		
Blood creatinine increased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Blood pressure increased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Blood thyroid stimulating hormone increased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Body temperature increased			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Alanine aminotransferase increased			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Weight decreased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	3		
Transaminases increased			

subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Lymphocyte count decreased			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Subdural haematoma			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Limb injury			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Ligament sprain			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Head injury			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Accident at home			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Wound dehiscence			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Skin wound			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Skin laceration			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Immunisation reaction			

subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Paraesthesia			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Migraine			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Lethargy			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	4		
Dizziness			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Sciatica			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia vitamin B12 deficiency			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Eosinophilia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Neutropenia			

subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Anaemia			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	3		
Thrombocytopenia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Leukopenia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Eye disorders			
Diplopia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Dry eye			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Retinal disorder			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Vision blurred			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Xerophthalmia			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Conjunctival suffusion			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Gastrointestinal disorders			

Abdominal distension				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Abdominal pain				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Gastrooesophageal reflux disease				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Dyspepsia				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Diarrhoea				
subjects affected / exposed	2 / 15 (13.33%)			
occurrences (all)	2			
Constipation				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Colitis				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Anal haemorrhage				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Abdominal pain upper				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	4			
Nausea				
subjects affected / exposed	4 / 15 (26.67%)			
occurrences (all)	9			
Vomiting				
subjects affected / exposed	2 / 15 (13.33%)			
occurrences (all)	2			
Toothache				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			

Stomatitis subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Rectal haemorrhage subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Haemorrhoids subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Gastritis subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Enteritis subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Dysphagia subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Dry mouth subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Change of bowel habit subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Hepatobiliary disorders Cholestasis subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Hepatic cytolysis subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Skin and subcutaneous tissue disorders Umbilical discharge subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Skin hypopigmentation			

subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Skin hyperplasia				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	4			
Scab				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Rash maculo-papular				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	2			
Rash				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Pruritus				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Hair colour changes				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Erythema				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Eczema				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Dry skin				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Dermatitis contact				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Alopecia				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Vitiligo				

subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	3		
Skin lesion			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Rash papular			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Rash macular			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Rash erythematous			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Psoriasis			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Lichen planus			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Dermatitis allergic			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Skin burning sensation			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Rash pruritic			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Pollakiuria			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		

Proteinuria			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Urethral dilatation			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Hypophysitis			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Hyperthyroidism			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Joint effusion			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Compartment syndrome			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Bone pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Arthritis			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Arthralgia			

subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	3		
Musculoskeletal chest pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Neck pain			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	3		
Rhabdomyolysis			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Rheumatic disorder			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Tendonitis			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Musculoskeletal stiffness			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Muscle spasms			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Joint stiffness			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Skin infection			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		

Tinea versicolour				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Rhinitis				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Cellulitis				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Cellulitis orbital				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Clostridium difficile infection				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Diarrhoea infectious				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Enterocolitis infectious				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Genital herpes simplex				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Herpes simplex				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Herpes simplex reactivation				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Herpes zoster				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			
Oral herpes				
subjects affected / exposed	0 / 15 (0.00%)			
occurrences (all)	0			

Respiratory tract infection subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Wound infection subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
COVID-19 subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Cystitis subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Dermatophytosis subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Vaginal infection subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Postoperative wound infection subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Fungal skin infection subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Mastoiditis subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Metabolism and nutrition disorders Hypomagnesaemia subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Hypokalaemia			

subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Hypocalcaemia			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Hyperglycaemia			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Gout			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Decreased appetite			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Hypophosphataemia			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Hyponatraemia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Hyperuricaemia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 July 2019	- Updated the protocol to "Subjects with stage IVM1d and up to 3 cerebral metastases may be enrolled, provided that all lesions have been adequately treated with stereotactic radiation therapy, craniotomy, or gamma knife therapy, with no evidence of progression and not requiring steroids for at least 2 months prior to enrollment.". - Added "Subsequent anticancer therapies will be collected from the end of investigational product administration through safety and survival follow-up until the subject ends study" - Added "Subjects with grade 2 endocrinopathies (ie, requiring replacement therapy only) may be enrolled upon review and approval by the medical monitor.". - Changed when concomitant medication was to be recorded from the safety follow-up during the follow-up period to the end of the study. - The investigator can no longer decide when discontinue treatment or a participant from the study. - Added disease stage (stage IVM1b or lower, stage IVM1c/d) at baseline to the covariate analysis. - Added 24-hour urine creatine clearance.
10 March 2020	- Added participants with prior treatment and disease progression on more than 1 line of anti-PD-1 therapy are excluded. - Added efficacy will also be performed Per Protocol Analysis Set (PPAS). The PPAS was defined as a subset of the full analysis set and includes participants who do not have important protocol deviations that are considered to have an impact on efficacy outcomes. - Added to lesion and efficacy assessment "Subjects who have reached a confirmed CR may increase their interval of radiographic assessments up to 6 months (26 weeks) after the first 2 years beyond confirmed CR and up to 12 months (52 weeks) after the first 5 years beyond confirmed CR as long as CR is maintained.". - Added an optional pharmacogenetic assessment. - Added an exploratory assessment of measuring the target lesions (visceral, injected, and uninjected non visceral). - Added that sperm donation within the prescribed period of time is prohibited. - Added the investigator must document the changes to the schedule of activities.

09 June 2021	- Added the number of participants (72 participants were enrolled with 27 participants in cohort 1 and 15 participants in cohorts 2, 3, and 4). - Updated language throughout the protocol to allow treatment with pembrolizumab to continue if a complete response was observed. - Safety reporting language updated for adherence to current Amgen standard operating procedures. - Immune-related adverse events updated to include neurological toxicities and exfoliative dermatologic conditions to align with the pembrolizumab Investigator Brochure. - Serious adverse events (SAEs) after the protocol-required reporting period, specifically participants ending study due to death, have not been reported as SAEs for other studies on the program. As a result, additional clarification was added to Section 9.2.3.1.1.3 - "Serious Adverse Events After the Protocol-required Reporting Period" and throughout the protocol for consistency to mitigate this. Furthermore, these changes align with Amgen's current protocol template and guidance. - Clarified that the visit windows are +/- 3 days during the treatment period, as operationally, it is more reasonable for sites to have the minus window. It was further noted that the week 0 visit was an exception, where the -3 days does not apply. All assessments for Week 0 should be completed following enrollment (via Interactive Response Technology), using the + 3-day window for the first dose. - Additionally, the visit window for radiographic assessments for participants who discontinued treatment for any reason other than confirmed iPD (by modified irRC-RECIST) was updated from 12 weeks (+ 1 week) to (+/- 1 week). - Minor clarifications added to align with the statistical analysis plan: - Clarified in Section 9.2.2.2-Modified RECIST v1.1, that "Following modified RECIST v1.1 tumor assessments will continue through to the first PD". - Physical Measurements removed from safety analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported