Clinical trial results:
A Phase 1b/3, Multicenter, Trial of Talimogene Laherparepvec in Combination With Pembrolizumab (MK-3475) for Treatment of Unresectable Stage IIIB to IVM1c Melanoma (MASTERKEY-265)

Summary

EudraCT number	2014-000185-22
Trial protocol	SE ES BE DE AT GR IT FI CZ PT HU
Global end of trial date	11 March 2021

Results information

Result version number	v1 (current)
This version publication date	24 March 2022
First version publication date	24 March 2022

Trial information

Trial identification

Sponsor protocol code	20110265

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02263508
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 March 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 March 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Phase 1b: To evaluate the safety, as assessed by incidence of dose limiting toxicity (DLT), of talimogene laherparepvec (T-VEC) in combination with pembrolizumab in subjects with previously untreated, unresectable, stage IIIB to IVM1c melanoma.
Phase 3: To evaluate the efficacy of talimogene laherparepvec with pembrolizumab versus placebo with pembrolizumab, as assessed by progression-free survival (PFS) (response evaluation by blinded independent central review [BICR] using modified Response Evaluation Criteria in Solid Tumors [RECIST] 1.1) and overall survival (OS).

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 December 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	60 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 76
Country: Number of subjects enrolled	Austria: 18
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Canada: 12
Country: Number of subjects enrolled	Czechia: 43
Country: Number of subjects enrolled	Finland: 4
Country: Number of subjects enrolled	France: 24
Country: Number of subjects enrolled	Germany: 74
Country: Number of subjects enrolled	Greece: 43
Country: Number of subjects enrolled	Hungary: 8
Country: Number of subjects enrolled	Italy: 17
Country: Number of subjects enrolled	Korea, Republic of: 11

Country: Number of subjects enrolled	Netherlands: 13
Country: Number of subjects enrolled	Poland: 53
Country: Number of subjects enrolled	Portugal: 11
Country: Number of subjects enrolled	Russian Federation: 39
Country: Number of subjects enrolled	South Africa: 35
Country: Number of subjects enrolled	Spain: 23
Country: Number of subjects enrolled	Switzerland: 21
Country: Number of subjects enrolled	United Kingdom: 18
Country: Number of subjects enrolled	United States: 166
Worldwide total number of subjects	713
EEA total number of subjects	335

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)	368
From 65 to 84 years	313
85 years and over	32

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 134 centers in Australia, Canada, Europe, South Africa, South Korea, and the United States.
Phase 1b was an open-label, single-arm study and Phase 3 was a randomized, double-blind, placebo-controlled study.

Pre-assignment

Screening details:

In Phase 3 participants were randomized equally to 1 of 2 arms.
Randomization was stratified by stage of disease: less advanced stages (IIIB, IIIC, and IVM1a) versus more advanced stages (IVM1b and IVM1c) and by prior BRAF inhibitor therapy (no prior BRAF inhibitor vs BRAF inhibitor with or without MEK inhibitor).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase 1b: Talimogene Laherparepvec + Pembrolizumab

Arm description:

Participants received talimogene laherparepvec at an initial dose of up to 4 mL 10 plaque-forming units (PFU)/mL by intralesional injection on day 1 of week 1. Subsequent doses of talimogene laherparepvec at up to 4 mL of 10^8 PFU/mL began 3 weeks after the first dose and were administered every 2 weeks until disappearance of injectable lesions, complete response (CR), confirmed disease progression (PD) per modified Immune-related Response Criteria (irRC), intolerance of study treatment, 24 months from the date of the first dose of pembrolizumab, or end of study, whichever occurred first. Participants also received 200 mg pembrolizumab administered intravenously every 2 weeks starting at the time of the third dose of talimogene laherparepvec (week 6) until confirmed PD per modified irRC, treatment intolerance, 24 months from the first dose, or end of study, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Talimogene Laherparepvec
Investigational medicinal product code	AMG 678
Other name	IMLYGIC®, OncoVEX^GM-CSF, T-VEC
Pharmaceutical forms	Solution for injection
Routes of administration	Intralesional use

Dosage and administration details:

Talimogene laherparepvec administered by intratumoral injection at an initial dose of up to 4 mL 10 plaque-forming units (PFU)/mL followed by up to 4 mL of 10^8 PFU/mL 3 weeks later and every 2 weeks thereafter.

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:

Administered at a dose of 200 mg as an intravenous infusion over approximately 30 minutes.

Arm title	Phase 3: Placebo + Pembrolizumab

Arm description:

Participants received up to 4 mL placebo to talimogene laherparepvec by intralesional injection on day 1

of week 0. Subsequent doses of placebo (up to 4 mL) began 3 weeks after the first dose and were administered every 2 weeks until the fifth injection (week 9), and then synchronously with pembrolizumab thereafter every 3 weeks until disappearance of injectable lesions, complete response per modified Immune-related Response Criteria simulating Response Evaluation Criteria in Solid Tumors (irRC-RECIST) (iCR), confirmed iPD per modified irRC-RECIST, intolerance of study treatment, 24 months from the date of the first dose of placebo, or end of study, whichever occurred first. Participants also received 200 mg pembrolizumab administered intravenously every 3 weeks starting on day 1 of week 0, until confirmed iPD per modified irRC-RECIST, treatment intolerance, 24 months from the first dose, or end of study, whichever occurred first.

Arm type	Active comparator
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:

Administered at a dose of 200 mg as an intravenous infusion over approximately 30 minutes.

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

Dosage and administration details:

Administered by intratumoral injection at an initial dose of up to 4 mL followed by up to 4 mL 3 weeks later and every 2 weeks thereafter.

Arm title	Phase 3: Talimogene Laherparepvec + Pembrolizumab

Arm description:

Participants received talimogene laherparepvec at an initial dose of up to 4 mL 10 PFU/mL by intralesional injection on day 1. Subsequent doses of talimogene laherparepvec at 10^8 PFU/mL (up to 4 mL) began 3 weeks after the first dose and were administered every 2 weeks until the fifth injection of talimogene laherparepvec (week 9), and then synchronously with pembrolizumab thereafter every 3 weeks until disappearance of injectable lesions, iCR, confirmed iPD per modified irRC-RECIST, intolerance of study treatment, 24 months from the date of the first dose of talimogene laherparepvec, or end of study, whichever occurred first. Participants also received 200 mg pembrolizumab administered intravenously every 3 weeks starting on day 1 of week 0, until confirmed iPD per modified irRC-RECIST, treatment intolerance, 24 months from the first dose, or end of study, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Talimogene Laherparepvec
Investigational medicinal product code	AMG 678
Other name	IMLYGIC®, OncoVEX^GM-CSF, T-VEC
Pharmaceutical forms	Solution for injection
Routes of administration	Intralesional use

Dosage and administration details:

Talimogene laherparepvec administered by intratumoral injection at an initial dose of up to 4 mL 10 plaque-forming units (PFU)/mL followed by up to 4 mL of 10^8 PFU/mL 3 weeks later and every 2 weeks thereafter.

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:

Administered at a dose of 200 mg as an intravenous infusion over approximately 30 minutes.

Number of subjects in period 1	Phase 1b: Talimogene Laherparepvec + Pembrolizumab	Phase 3: Placebo + Pembrolizumab	Phase 3: Talimogene Laherparepvec + Pembrolizumab
Started	21	346	346
Received T-VEC/Placebo	21	345	343
Received Pembrolizumab	21	345	343
Completed	0	0	0
Not completed	21	346	346
Adverse event, serious fatal	6	151	140
Consent withdrawn by subject	1	23	17
Sponsor Decision	12	165	182
Lost to follow-up	2	7	7

Baseline characteristics

Reporting groups

Reporting group title	Phase 1b: Talimogene Laherparepvec + Pembrolizumab

Reporting group description:

Participants received talimogene laherparepvec at an initial dose of up to 4 mL 10 plaque-forming units (PFU)/mL by intralesional injection on day 1 of week 1. Subsequent doses of talimogene laherparepvec at up to 4 mL of 10^8 PFU/mL began 3 weeks after the first dose and were administered every 2 weeks until disappearance of injectable lesions, complete response (CR), confirmed disease progression (PD) per modified Immune-related Response Criteria (irRC), intolerance of study treatment, 24 months from the date of the first dose of pembrolizumab, or end of study, whichever occurred first. Participants also received 200 mg pembrolizumab administered intravenously every 2 weeks starting at the time of the third dose of talimogene laherparepvec (week 6) until confirmed PD per modified irRC, treatment intolerance, 24 months from the first dose, or end of study, whichever occurred first.

Reporting group title	Phase 3: Placebo + Pembrolizumab

Reporting group description:

Participants received up to 4 mL placebo to talimogene laherparepvec by intralesional injection on day 1 of week 0. Subsequent doses of placebo (up to 4 mL) began 3 weeks after the first dose and were administered every 2 weeks until the fifth injection (week 9), and then synchronously with pembrolizumab thereafter every 3 weeks until disappearance of injectable lesions, complete response per modified Immune-related Response Criteria simulating Response Evaluation Criteria in Solid Tumors (irRC-RECIST) (iCR), confirmed iPD per modified irRC-RECIST, intolerance of study treatment, 24 months from the date of the first dose of placebo, or end of study, whichever occurred first. Participants also received 200 mg pembrolizumab administered intravenously every 3 weeks starting on day 1 of week 0, until confirmed iPD per modified irRC-RECIST, treatment intolerance, 24 months from the first dose, or end of study, whichever occurred first.

Reporting group title	Phase 3: Talimogene Laherparepvec + Pembrolizumab

Reporting group description:

Participants received talimogene laherparepvec at an initial dose of up to 4 mL 10 PFU/mL by intralesional injection on day 1. Subsequent doses of talimogene laherparepvec at 10^8 PFU/mL (up to 4 mL) began 3 weeks after the first dose and were administered every 2 weeks until the fifth injection of talimogene laherparepvec (week 9), and then synchronously with pembrolizumab thereafter every 3 weeks until disappearance of injectable lesions, iCR, confirmed iPD per modified irRC-RECIST, intolerance of study treatment, 24 months from the date of the first dose of talimogene laherparepvec, or end of study, whichever occurred first. Participants also received 200 mg pembrolizumab administered intravenously every 3 weeks starting on day 1 of week 0, until confirmed iPD per modified irRC-RECIST, treatment intolerance, 24 months from the first dose, or end of study, whichever occurred first.

Reporting group values	Phase 1b: Talimogene Laherparepvec + Pembrolizumab	Phase 3: Placebo + Pembrolizumab	Phase 3: Talimogene Laherparepvec + Pembrolizumab
Number of subjects	21	346	346
Age categorical Units: Subjects			
Adults (18-64 years)	14	177	177
From 65-84 years	6	157	150
85 years and over	1	12	19
Age Continuous Units: years			
arithmetic mean	60.2	62.3	63.1
standard deviation	± 13.4	± 14.5	± 13.7
Sex: Female, Male Units: participants			
Female	13	127	147
Male	8	219	199

Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	9	13
Not Hispanic or Latino	21	337	331
Unknown or Not Reported	0	0	2
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	4	7
Black (or African American)	0	1	2
Native Hawaiian or Other Pacific Islander	0	0	0
White	21	335	327
Other	0	6	10
Disease Stage per the American Joint Committee on Cancer (AJCC) 7th Edition			
Stage IIIB: Ulcerated lesion and 1 lymph node or 2-3 nodes with micrometastasis, or any-depth lesion with no ulceration, and 1 lymph node or 2-3 nodes with macrometastasis; Stage IIIC: Ulcerated lesion and 1 lymph node with macrometastasis; 2-3 nodes with macrometastasis or ≥4 metastatic lymph nodes, matted lymph nodes, or in-transit met(s)/satellite(s); Stage IV: M1a: Spread to skin, subcutaneous tissue, or lymph nodes; normal lactate dehydrogenase (LDH) level; M1b: Spread to lungs, normal LDH; M1c: Spread to all other visceral organs, normal LDH or any distant disease with elevated LDH.			
Units: Subjects			
Stage IIIB - IVM1a	9	169	169
Stage IVM1b/c	12	177	177
Prior Serine/Threonine Protein Kinase B-Raf (BRAF) Inhibitor Therapy Units: Subjects			
Yes	0	29	29
No	0	317	317
Not collected	21	0	0
Programmed Cell Death-1 Ligand 1 (PD-L1) Status			
PD-L1 expression in tumor cells was assessed at a central laboratory using a clinical trial immunohistochemistry assay (22C3 antibody) and scored on a unique melanoma (MEL) scale of 0 to 5; a score ≥ 2 (membranous staining in ≥ 1% of cells within tumor nests, including neoplastic cells and intercalated and contiguous immune cells) was considered positive.			
Units: Subjects			
Positive	17	218	231
Not Positive	4	128	115
BRAF V600 Mutation Status			
Mutation status of v-raf murine sarcoma viral oncogene homolog B1 (BRAF) gene was based on a gene mutation that results in an amino acid substitution from valine (V) to glutamic acid (E) at codon 600 (V600E) and/or a substitution from valine to lysine (K) (V600K).			
Units: Subjects			
Mutation	4	116	124
Mutation not present	17	215	211
Missing/unknown	0	15	11

Reporting group values	Total		
Number of subjects	713		
Age categorical Units: Subjects			
Adults (18-64 years)	368		
From 65-84 years	313		

85 years and over	32		

Age Continuous Units: years arithmetic mean standard deviation	- -		
Sex: Female, Male Units: participants			
Female	287		
Male	426		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	22		
Not Hispanic or Latino	689		
Unknown or Not Reported	2		
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	0		
Asian	11		
Black (or African American)	3		
Native Hawaiian or Other Pacific Islander	0		
White	683		
Other	16		
Disease Stage per the American Joint Committee on Cancer (AJCC) 7th Edition			
Stage IIIB: Ulcerated lesion and 1 lymph node or 2-3 nodes with micrometastasis, or any-depth lesion with no ulceration, and 1 lymph node or 2-3 nodes with macrometastasis; Stage IIIC: Ulcerated lesion and 1 lymph node with macrometastasis; 2-3 nodes with macrometastasis or ≥4 metastatic lymph nodes, matted lymph nodes, or in-transit met(s)/satellite(s); Stage IV: M1a: Spread to skin, subcutaneous tissue, or lymph nodes; normal lactate dehydrogenase (LDH) level; M1b: Spread to lungs, normal LDH; M1c: Spread to all other visceral organs, normal LDH or any distant disease with elevated LDH.			
Units: Subjects			
Stage IIIB - IVM1a	347		
Stage IVM1b/c	366		
Prior Serine/Threonine Protein Kinase B-Raf (BRAF) Inhibitor Therapy Units: Subjects			
Yes	58		
No	634		
Not collected	21		
Programmed Cell Death-1 Ligand 1 (PD-L1) Status			
PD-L1 expression in tumor cells was assessed at a central laboratory using a clinical trial immunohistochemistry assay (22C3 antibody) and scored on a unique melanoma (MEL) scale of 0 to 5; a score ≥ 2 (membranous staining in ≥ 1% of cells within tumor nests, including neoplastic cells and intercalated and contiguous immune cells) was considered positive.			
Units: Subjects			
Positive	466		
Not Positive	247		
BRAF V600 Mutation Status			
Mutation status of v-raf murine sarcoma viral oncogene homolog B1 (BRAF) gene was based on a gene mutation that results in an amino acid substitution from valine (V) to glutamic acid (E) at codon 600			

(V600E) and/or a substitution from valine to lysine (K) (V600K).			
Units: Subjects			
Mutation	244		
Mutation not present	443		
Missing/unknown	26		

End points

End points reporting groups

Reporting group title	Phase 1b: Talimogene Laherparepvec + Pembrolizumab

Reporting group description:

Participants received talimogene laherparepvec at an initial dose of up to 4 mL 10 plaque-forming units (PFU)/mL by intralesional injection on day 1 of week 1. Subsequent doses of talimogene laherparepvec at up to 4 mL of 10^8 PFU/mL began 3 weeks after the first dose and were administered every 2 weeks until disappearance of injectable lesions, complete response (CR), confirmed disease progression (PD) per modified Immune-related Response Criteria (irRC), intolerance of study treatment, 24 months from the date of the first dose of pembrolizumab, or end of study, whichever occurred first. Participants also received 200 mg pembrolizumab administered intravenously every 2 weeks starting at the time of the third dose of talimogene laherparepvec (week 6) until confirmed PD per modified irRC, treatment intolerance, 24 months from the first dose, or end of study, whichever occurred first.

Reporting group title	Phase 3: Placebo + Pembrolizumab

Reporting group description:

Participants received up to 4 mL placebo to talimogene laherparepvec by intralesional injection on day 1 of week 0. Subsequent doses of placebo (up to 4 mL) began 3 weeks after the first dose and were administered every 2 weeks until the fifth injection (week 9), and then synchronously with pembrolizumab thereafter every 3 weeks until disappearance of injectable lesions, complete response per modified Immune-related Response Criteria simulating Response Evaluation Criteria in Solid Tumors (irRC-RECIST) (iCR), confirmed iPD per modified irRC-RECIST, intolerance of study treatment, 24 months from the date of the first dose of placebo, or end of study, whichever occurred first. Participants also received 200 mg pembrolizumab administered intravenously every 3 weeks starting on day 1 of week 0, until confirmed iPD per modified irRC-RECIST, treatment intolerance, 24 months from the first dose, or end of study, whichever occurred first.

Reporting group title	Phase 3: Talimogene Laherparepvec + Pembrolizumab

Reporting group description:

Participants received talimogene laherparepvec at an initial dose of up to 4 mL 10 PFU/mL by intralesional injection on day 1. Subsequent doses of talimogene laherparepvec at 10^8 PFU/mL (up to 4 mL) began 3 weeks after the first dose and were administered every 2 weeks until the fifth injection of talimogene laherparepvec (week 9), and then synchronously with pembrolizumab thereafter every 3 weeks until disappearance of injectable lesions, iCR, confirmed iPD per modified irRC-RECIST, intolerance of study treatment, 24 months from the date of the first dose of talimogene laherparepvec, or end of study, whichever occurred first. Participants also received 200 mg pembrolizumab administered intravenously every 3 weeks starting on day 1 of week 0, until confirmed iPD per modified irRC-RECIST, treatment intolerance, 24 months from the first dose, or end of study, whichever occurred first.

Primary: Phase 1b: Number of Participants With Dose-limiting Toxicities (DLTs)

End point title	Phase 1b: Number of Participants With Dose-limiting Toxicities (DLTs)[1][2]

End point description:

A DLT was defined as any toxicity related to study drug which met any of the following criteria based on Common Terminology Criteria for Adverse Events (CTCAE) version 4.0:
-Grade 4 non-hematologic toxicity.
-Grade 3 or higher pneumonitis.
-Grade 3 non-hematologic toxicity lasting > 3 days despite optimal supportive care, excluding grade 3 fatigue.
-Any grade 3 or higher non-hematologic laboratory value if medical intervention was required, or the abnormality lead to hospitalization, or the abnormality persisted for > 1 week.
-Febrile neutropenia grade 3 or 4.
-Thrombocytopenia < 25 x 10^9/L if associated with a bleeding event which does not result in hemodynamic instability but required an elective platelet infusion, or a life-threatening bleeding event which resulted in urgent intervention and admission to intensive care unit.
-Grade 5 toxicity (ie, death).
-Any other intolerable toxicity leading to permanent discontinuation of talimogene laherparepvec or pembrolizumab.

End point type	Primary

End point timeframe:

The DLT evaluation period was 6 weeks from the initial administration of pembrolizumab (week 6 to 12).

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: Statistical analyses were not conducted in Phase 1b

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was pre-specified for Phase 1b participants only.

End point values	Phase 1b: Talimogene Laherparepvec + Pembrolizumab			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: participants	0			

Statistical analyses

No statistical analyses for this end point

Primary: Phase 3: Progression Free Survival (PFS) by Blinded Independent Central Review Assessed Using Modified RECIST 1.1

End point title	Phase 3: Progression Free Survival (PFS) by Blinded Independent Central Review Assessed Using Modified RECIST 1.1[3]

End point description:

PFS per modified Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 is defined as the interval from randomization to the earlier event of progressive disease (PD) per modified RECIST 1.1 or death from any cause.
PD: Increase in size of target lesions from nadir by ≥ 20% and ≥ 5 mm absolute increase above nadir, or the appearance of a new lesion.
Median PFS was calculated using the Kaplan-Meier method. Participants without an event were censored at their last evaluable tumor assessment if available; otherwise on their randomization date.
The primary analysis of PFS was specified to be conducted when 407 PFS events had occurred (data cut-off date 02 March 2020).

End point type	Primary

End point timeframe:

From randomization until the data-cut-off date of 02 March 2020; median (range) time on follow-up was 25.5 (0.6, 44.7) months in the Placebo + Pembrolizumab arm and 25.6 (0.3, 45.8) months in the Talimogene Laherparepvec + Pembrolizumab arm.

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was pre-specified for Phase 3 participants only.

End point values	Phase 3: Placebo + Pembrolizumab	Phase 3: Talimogene Laherparepvec + Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	346	346		
Units: months				

median (confidence interval 95%)	8.5 (5.72 to 13.54)	14.3 (10.25 to 22.11)		

Statistical analyses

Statistical analysis title	Analysis of PFS
Comparison groups	Phase 3: Placebo + Pembrolizumab v Phase 3: Talimogene Laherparepvec + Pembrolizumab
Number of subjects included in analysis	692
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.13 [4]
Method	Stratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.04

Notes:

[4] - Log-rank test stratified by randomization factors (disease stage, prior BRAF inhibitor therapy) and baseline PD-L1 status.

Primary: Phase 3: Overall Survival

End point title	Phase 3: Overall Survival[5]

End point description:

Overall survival (OS) is defined as the interval from randomization to death from any cause.
Median overall survival was calculated using the Kaplan-Meier method. Participants without an event were censored at their last known alive date. "99999" indicates values that could not be estimated due to the low number of events.

End point type	Primary

End point timeframe:

From randomization until the end of study; median (range) time on follow-up was 34.8 (0.6, 58.3) months in the Placebo + Pembrolizumab arm and 36.8 (0.3, 58.4) months in the Talimogene Laherparepvec + Pembrolizumab arm.

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was pre-specified for Phase 3 participants only.

End point values	Phase 3: Placebo + Pembrolizumab	Phase 3: Talimogene Laherparepvec + Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	346	346		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	Analysis of OS
Comparison groups	Phase 3: Placebo + Pembrolizumab v Phase 3: Talimogene Laherparepvec + Pembrolizumab
Number of subjects included in analysis	692
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.77 [6]
Method	Stratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	1.21

Notes:

[6] - Log-rank test stratified by randomization factors (disease stage, prior BRAF inhibitor therapy) and baseline PD-L1 status.

Secondary: Phase 1b: Objective Response Rate (ORR)

End point title	Phase 1b: Objective Response Rate (ORR)[7]

End point description:

ORR is defined as the percentage of participants with a best overall response of complete response (CR) or partial response (PR) using the modified Immune-related Response Criteria (irRC), by Investigator assessment.
CR was defined as the disappearance of all lesions; PR was defined as a decrease in tumor area ≥ 50% relative to baseline, response must have been confirmed by a second, consecutive assessment at least 4 weeks apart.
Radiographic imaging for assessment of lesions was performed using computed tomography (CT), positron emission tomography (PET), magnetic resonance imaging (MRI), or ultrasound. Clinical measurement of cutaneous, subcutaneous, and palpable nodal tumor lesions was conducted with calipers.

End point type	Secondary

End point timeframe:

Tumor assessments were performed at week 6 (prior to initiation of pembrolizumab), week 18, and every 12 weeks thereafter until confirmed PD or start of new anticancer treatment; median (range) time on follow-up was 58.6 (1.4, 61.6) months.

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was pre-specified for Phase 1b participants only.

End point values	Phase 1b: Talimogene Laherparepvec + Pembrolizumab			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: percentage of participants				
number (confidence interval 95%)	61.9 (38.4 to 81.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b: Best Overall Response (BOR)

End point title	Phase 1b: Best Overall Response (BOR)[8]

End point description:

Best overall response is defined as the best overall visit response in the following order: CR, PR, stable disease (SD), progressive disease (PD), or unevaluable (UE), based on investigator assessment using the modified irRC up to the start of any subsequent anti-cancer therapy.
CR was defined as the disappearance of all lesions; PR was defined as a decrease in tumor area ≥ 50% relative to baseline; PD was defined as an increase in tumor area ≥ 25% relative to nadir; and SD was defined as any outcome not meeting the criteria for response or PD with ≥ 77 days elapsed after enrollment. Responses and PD must have been confirmed by a second, consecutive assessment at least 4 weeks apart.

End point type	Secondary

End point timeframe:

Tumor assessments were performed at week 6 (prior to initiation of pembrolizumab), week 18, and every 12 weeks thereafter until confirmed PD or start of new anticancer treatment; median (range) time on follow-up was 58.6 (1.4, 61.6) months.

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was pre-specified for Phase 1b participants only.

End point values	Phase 1b: Talimogene Laherparepvec + Pembrolizumab			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: participants				
Complete Response (CR)	9			
Partial Response (PR)	4			
Stable Disease (SD)	1			
Progressive Disease (PD)	6			
Unable to Evaluate (UE)	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b: Durable Response Rate (DRR)

End point title	Phase 1b: Durable Response Rate (DRR)[9]

End point description:

DRR is defined as the percentage of participants with a best overall response of CR or PR using the modified irRC per Investigator assessment with a duration of response of at least 6 months.
CR was defined as the disappearance of all lesions; PR was defined as a decrease in tumor area ≥ 50% relative to baseline, response must have been confirmed by a second, consecutive assessment at least 4 weeks apart.

End point type	Secondary

End point timeframe:

Tumor assessments were performed at week 6 (prior to initiation of pembrolizumab), week 18, and every 12 weeks thereafter until confirmed PD or start of new anticancer treatment; median (range) time on follow-up was 58.6 (1.4, 61.6) months.

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was pre-specified for Phase 1b participants only.

End point values	Phase 1b: Talimogene Laherparepvec + Pembrolizumab			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: percentage of participants				
number (confidence interval 95%)	57.1 (34.0 to 78.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b: Duration of Response (DOR)

End point title	Phase 1b: Duration of Response (DOR)[10]

End point description:

Duration of response (DOR) is defined as the time from the date of an initial response (CR or PR) that is subsequently confirmed to the earlier of confirmed PD or death. Participants who had not ended their response at the time of analysis were censored at their last evaluable tumor assessment before start of the first subsequent anticancer therapy. "99999" indicates values that could not be estimated due to the low number of events.

CR was defined as the disappearance of all lesions; PR was defined as a decrease in tumor area ≥ 50% relative to baseline; PD was defined as an increase in tumor area ≥ 25% relative to nadir. Response and PD must have been confirmed by a second, consecutive assessment at least 4 weeks apart.

End point type	Secondary

End point timeframe:

Tumor assessments were performed at week 6 (prior to initiation of pembrolizumab), week 18, and every 12 weeks thereafter until confirmed PD or start of new anticancer treatment; median (range) time on follow-up was 58.6 (1.4, 61.6) months.

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was pre-specified for Phase 1b participants only.

End point values	Phase 1b: Talimogene Laherparepvec + Pembrolizumab			
Subject group type	Reporting group			
Number of subjects analysed	13[11]			
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)			

Notes:

[11] - Participants enrolled in Phase 1b who received ≥ 1 dose of study drug with a CR or PR.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b: Disease Control Rate (DCR)

End point title	Phase 1b: Disease Control Rate (DCR)[12]

End point description:

DCR is defined as the percentage of participants with a best overall response of CR, PR, or SD using the modified irRC per Investigator assessment.
CR was defined as the disappearance of all lesions; PR was defined as a decrease in tumor area ≥ 50% relative to baseline, response must have been confirmed by a second, consecutive assessment at least 4 weeks apart; and SD was defined as any outcome not meeting the criteria for response or PD with ≥ 84 days elapsed after enrollment.

End point type	Secondary

End point timeframe:

Tumor assessments were performed at week 6 (prior to initiation of pembrolizumab), week 18, and every 12 weeks thereafter until confirmed PD or start of new anticancer treatment; median (range) time on follow-up was 58.6 (1.4, 61.6) months.

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was pre-specified for Phase 1b participants only.

End point values	Phase 1b: Talimogene Laherparepvec + Pembrolizumab			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: percentage of participants				
number (confidence interval 95%)	66.7 (43.0 to 85.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b: Overall Survival (OS)

End point title	Phase 1b: Overall Survival (OS)[13]

End point description:

Overall survival is defined as the interval from first dose to death from any cause.
OS was estimated using the Kaplan-Meier method. Participants without an event were censored at their last known alive date. "99999" indicates values that could not be estimated due to the low number of events.

End point type	Secondary

End point timeframe:

From first dose until the end of study; median (range) time on follow-up was 70.6 (1.4, 74.5) months.

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was pre-specified for Phase 1b participants only.

End point values	Phase 1b: Talimogene Laherparepvec + Pembrolizumab			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b: Progression-free Survival (PFS)

End point title	Phase 1b: Progression-free Survival (PFS)[14]

End point description:

Progression-free survival is defined as the time from first dose to the earlier event of confirmed PD per modified irRC or death from any cause. PFS was estimated using the Kaplan-Meier method. Participants without an event were censored at their last evaluable tumor assessment. "99999" indicates values that could not be estimated due to the low number of events.

End point type	Secondary

End point timeframe:

From first dose until the end of study; median (range) time on follow-up was 70.6 (1.4, 74.5) months.

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was pre-specified for Phase 1b participants only.

End point values	Phase 1b: Talimogene Laherparepvec + Pembrolizumab			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 3: Complete Response Rate Assessed Using Modified irRC-RECIST (iCRR)

End point title	Phase 3: Complete Response Rate Assessed Using Modified irRC-RECIST (iCRR)[15]

End point description:

Complete response rate per modified Immune-related Response Criteria (irRC) simulating RECIST 1.1 (irRC-RECIST) is defined as the percentage of participants with a best overall response of complete response assessed using the modified irRC-RECIST (iCR) evaluated by blinded independent central review.

iCR: Disappearance of all lesions (whether measurable or not and whether baseline or new) and confirmation by a repeat, consecutive assessment at least 4 weeks after the criteria were first met. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Modifications to the irRC-RECIST 1.1 included an increase in the total number of target lesions and new measurable lesions to 10 with a maximum of 5 target lesions per organ, and target lesions must have been measurable by CT or MRI only.

End point type	Secondary

End point timeframe:

Tumor assessments were performed every 12 weeks after initiation of treatment until confirmed PD or start of new anticancer treatment; median (range) time on follow-up was 30.6 (0.6, 53.0) months and 31.4 (0.3, 52.5) months in each group, respectively.

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was pre-specified for Phase 3 participants only.

End point values	Phase 3: Placebo + Pembrolizumab	Phase 3: Talimogene Laherparepvec + Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	346	346		
Units: percentage of participants				
number (confidence interval 95%)	8.1 (5.22 to 10.97)	14.5 (10.75 to 18.16)		

Statistical analyses

Statistical analysis title	Analysis of iCRR
Comparison groups	Phase 3: Placebo + Pembrolizumab v Phase 3: Talimogene Laherparepvec + Pembrolizumab
Number of subjects included in analysis	692
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.012 [16]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.15
upper limit	3.07

Notes:

[16] - Logistic regression stratified by randomization stratification factors (disease stage and prior BRAF inhibitor therapy) and the baseline PD-L1 status.

Secondary: Phase 3: Progression Free Survival Assessed Using Modified irRC-RECIST (iPFS)

End point title	Phase 3: Progression Free Survival Assessed Using Modified irRC-RECIST (iPFS)[17]

End point description:

PFS per modified irRC-RECIST is defined as the interval from randomization to the earlier event of progressive disease assessed by modified irRC-RECIST (iPD) evaluated by blinded independent central review, or death from any cause.
iPD: Increase in tumor burden ≥ 20% and at least 5 mm absolute increase relative to nadir (minimum recorded tumor burden) confirmed by a repeat, consecutive assessment at least 4 weeks after the initial detection.
Median iPFS was calculated using the Kaplan-Meier method. Participants without an event were censored at their last evaluable tumor assessment if available; otherwise on their randomization date. "99999" indicates values that could not be estimated due to the low number of events.
The primary analysis of iPFS was specified to be conducted when 256 iPFS events had occurred (data cut-off date 29 September 2020).

End point type	Secondary

End point timeframe:

From randomization until the data cut-off date of 29 September 2020; median time on follow-up was 30.6 (0.6, 53.0) months in the Placebo + Pembrolizumab arm and 31.4 (0.3, 52.5) months in the Talimogene Laherparepvec + Pembrolizumab arm.

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was pre-specified for Phase 3 participants only.

End point values	Phase 3: Placebo + Pembrolizumab	Phase 3: Talimogene Laherparepvec + Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	346	346		
Units: months				
median (confidence interval 95%)	25.3 (17.68 to 99999)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	Analysis of iPFS
Comparison groups	Phase 3: Talimogene Laherparepvec + Pembrolizumab v Phase 3: Placebo + Pembrolizumab
Number of subjects included in analysis	692
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.14 [18]
Method	Stratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	1.34

Notes:

[18] - Log-rank test stratified by randomization factors (disease stage, prior BRAF inhibitor therapy) and baseline PD-L1 status.

Secondary: Phase 3: Overall Survival Excluding Stage IVM1c Participants

End point title	Phase 3: Overall Survival Excluding Stage IVM1c Participants[19]

End point description:

Overall survival is defined as the interval from randomization to death from any cause.
Median OS was calculated using the Kaplan-Meier method. Participants without an event were censored at the last known alive date. "99999" indicates values that could not be estimated due to the low number of events.

End point type	Secondary

End point timeframe:

From randomization until the end of study; median (range) time on follow-up was 34.8 (0.6, 58.3) months in the Placebo + Pembrolizumab arm and 36.8 (0.3, 58.4) months in the Talimogene Laherparepvec + Pembrolizumab arm.

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was pre-specified for Phase 3 participants only.

End point values	Phase 3: Placebo + Pembrolizumab	Phase 3: Talimogene Laherparepvec + Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	203[20]	201[21]		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Notes:

[20] - Participants randomized in Phase 3 with stage IIIB to IVM1a/b.

[21] - Participants randomized in Phase 3 with stage IIIB to IVM1a/b.

Statistical analyses

Statistical analysis title	Analysis of OS Excluding Stage IVM1c Participants
Comparison groups	Phase 3: Placebo + Pembrolizumab v Phase 3: Talimogene Laherparepvec + Pembrolizumab
Number of subjects included in analysis	404
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.47 [22]
Method	Stratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	1.24

Notes:

[22] - Log-rank test stratified by randomization factors (disease stage, prior BRAF inhibitor therapy) and baseline PD-L1 status.

Secondary: Phase 3: Objective Response Rate Assessed Using Modified RECIST 1.1

End point title	Phase 3: Objective Response Rate Assessed Using Modified RECIST 1.1[23]

End point description:

ORR is defined as the percentage of participants with a best overall response of complete response (CR) or partial response (PR) assessed using modified RECIST version 1.1, evaluated by blinded independent central review.
CR was defined as the disappearance of all lesions except lymph node short axis < 10 mm; PR was defined as a ≥ 30% reduction in sum of diameters in target lesions. Confirmation of CR or PR was not required.

Modifications to conventional RECIST 1.1 included the following: target lesions were measurable on CT or MRI; otherwise, they were considered as nontarget lesions. A maximum of 10 target lesions was allowed with up to 5 per organ.

End point type	Secondary

End point timeframe:

Tumor assessments were performed every 12 weeks after initiation of treatment until confirmed PD or start of new anticancer treatment; median (range) time on follow-up was 30.6 (0.6, 53.0) months and 31.4 (0.3, 52.5) months in each group, respectively.

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was pre-specified for Phase 3 participants only.

End point values	Phase 3: Placebo + Pembrolizumab	Phase 3: Talimogene Laherparepvec + Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	346	346		
Units: percentage of participants				
number (confidence interval 95%)	41.3 (36.14 to 46.52)	48.6 (43.29 to 53.82)		

Statistical analyses

Statistical analysis title	Analysis of ORR
Comparison groups	Phase 3: Placebo + Pembrolizumab v Phase 3: Talimogene Laherparepvec + Pembrolizumab
Number of subjects included in analysis	692
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.081 [24]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.97
upper limit	1.79

Notes:

[24] - Logistic regression stratified by randomization stratification factors (disease stage and prior BRAF inhibitor therapy) and the baseline PD-L1 status.

Secondary: Phase 3: Best Overall Response Assessed Using Modified RECIST 1.1

End point title	Phase 3: Best Overall Response Assessed Using Modified RECIST 1.1[25]

End point description:

Best overall response is defined as the best overall visit response up to and including the first overall visit response of PD in the following order: CR, PR, SD, non-CR/Non-PD (NN), PD or UE assessed using modified RECIST version 1.1, evaluated by blinded independent central review.
CR was defined as the disappearance of all lesions except lymph node short axis < 10 mm; PR was defined as a ≥ 30% reduction in sum of diameters in target lesions. Confirmation of CR or PR was not required. NN was defined as persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits. SD was defined as neither sufficient shrinkage of target lesions to qualify for CR or PR nor sufficient increase to qualify for PD with ≥ 84 days elapsed after randomization. PD was defined as an increase from nadir by ≥ 20% or ≥ 5 mm absolute increase above nadir of target lesions or appearance of any new lesion.

End point type	Secondary

End point timeframe:

Tumor assessments were performed every 12 weeks after initiation of treatment until confirmed PD or start of new anticancer treatment; median (range) time on follow-up was 30.6 (0.6, 53.0) months and 31.4 (0.3, 52.5) months in each group, respectively.

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was pre-specified for Phase 3 participants only.

End point values	Phase 3: Placebo + Pembrolizumab	Phase 3: Talimogene Laherparepvec + Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	346	346		
Units: participants				
Complete response (CR)	40	62		
Partial response (PR)	103	106		
Stable disease (SD)	30	28		
Non-CR/Non-PD (NN)	16	11		
Progressive disease (PD)	120	106		
Unevaluable (UE)	11	3		
Not done	26	30		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 3: Durable Response Rate (DRR) Assessed Using Modified RECIST 1.1

End point title	Phase 3: Durable Response Rate (DRR) Assessed Using Modified RECIST 1.1[26]

End point description:

DRR is defined as the percentage of participants with a CR or PR per modified RECIST 1.1 and evaluated by blinded independent central review with a duration of response for ≥ 6 months.

End point type	Secondary

End point timeframe:

Tumor assessments were performed every 12 weeks after initiation of treatment until confirmed PD or start of new anticancer treatment; median (range) time on follow-up was 30.6 (0.6, 53.0) months and 31.4 (0.3, 52.5) months in each group, respectively.

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was pre-specified for Phase 3 participants only.

End point values	Phase 3: Placebo + Pembrolizumab	Phase 3: Talimogene Laherparepvec + Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	346	346		
Units: percentage of participants				
number (confidence interval 95%)	34.1 (29.11 to 39.10)	42.2 (36.99 to 47.40)		

Statistical analyses

Statistical analysis title	Analysis of DRR
Comparison groups	Phase 3: Placebo + Pembrolizumab v Phase 3: Talimogene Laherparepvec + Pembrolizumab
Number of subjects included in analysis	692
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.039 [27]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.02
upper limit	1.9

Notes:

[27] - Logistic regression stratified by randomization stratification factors (disease stage and prior BRAF inhibitor therapy) and the baseline PD-L1 status.

Secondary: Phase 3: Duration of Response (DOR) Assessed Using Modified RECIST 1.1

End point title	Phase 3: Duration of Response (DOR) Assessed Using Modified RECIST 1.1[28]

End point description:

Duration of response (DOR) is defined as the time from the date of an initial response of CR or PR to the earlier of PD per modified RECIST 1.1, or death. Participants who had not ended their response at the time of analysis were censored at their last evaluable tumor assessment date before start of the first subsequent anticancer therapy. "99999" indicates values that could not be estimated due to the low number of events.

End point type	Secondary

End point timeframe:

From randomization until the data cut-off date of 29 September 2020; median time on follow-up was 30.6 (0.6, 53.0) months in the Placebo + Pembrolizumab arm and 31.4 (0.3, 52.5) months in the Talimogene Laherparepvec + Pembrolizumab arm.

Notes:

[28] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was pre-specified for Phase 3 participants only.

End point values	Phase 3: Placebo + Pembrolizumab	Phase 3: Talimogene Laherparepvec + Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143	168		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	43.7 (-99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 3: Disease Control Rate (DCR) Assessed Using RECIST 1.1

End point title	Phase 3: Disease Control Rate (DCR) Assessed Using RECIST 1.1[29]

End point description:

Disease control rate (DCR) per modified RECIST 1.1 is defined as the percentage of participants with a best overall response of CR, PR or SD evaluated by blinded independent central review.
CR was defined as the disappearance of all lesions except lymph node short axis < 10 mm; PR was defined as a ≥ 30% reduction in sum of diameters in target lesions. Confirmation of CR or PR was not required. SD was defined as neither sufficient shrinkage of target lesions to qualify for CR or PR nor sufficient increase to qualify for PD with ≥ 84 days elapsed after randomization.

End point type	Secondary

End point timeframe:

Tumor assessments were performed every 12 weeks after initiation of treatment until confirmed PD or start of new anticancer treatment; median (range) time on follow-up was 30.6 (0.6, 53.0) months and 31.4 (0.3, 52.5) months in each group, respectively.

Notes:

[29] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was pre-specified for Phase 3 participants only.

End point values	Phase 3: Placebo + Pembrolizumab	Phase 3: Talimogene Laherparepvec + Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	346	346		
Units: percentage of participants				
number (confidence interval 95%)	50.0 (44.73 to 55.27)	56.6 (51.43 to 61.87)		

Statistical analyses

Statistical analysis title	Analysis of DCR
Comparison groups	Phase 3: Placebo + Pembrolizumab v Phase 3: Talimogene Laherparepvec + Pembrolizumab
Number of subjects included in analysis	692
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.11 [30]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.94
upper limit	1.75

Notes:

[30] - Logistic regression stratified by randomization stratification factors (disease stage and prior BRAF inhibitor therapy) and the baseline PD-L1 status.

Secondary: Phase 3: Objective Response Rate Assessed Using Modified irRC-RECIST (iORR)

End point title	Phase 3: Objective Response Rate Assessed Using Modified irRC-RECIST (iORR)[31]

End point description:

Objective response rate per modified irRC-RECIST is defined as the percentage of participants with a best overall response of iCR or partial response assessed using modified irRC-RECIST (iPR) evaluated by blinded independent central review.

iCR: Disappearance of all lesions (whether measurable or not and whether baseline or new) and confirmation by a repeat, consecutive assessment at least 4 weeks from the date first documented. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
iPR: Decrease in tumor burden ≥ 30% relative to baseline confirmed by a consecutive assessment at least 4 weeks after first documentation.

Modifications to the irRC-RECIST 1.1 included an increase in the total number of target lesions and new measurable lesions to 10 with a maximum of 5 target lesions per organ, and target lesions must be measurable by CT or MRI only.

End point type	Secondary

End point timeframe:

Tumor assessments were performed every 12 weeks after initiation of treatment until confirmed PD or start of new anticancer treatment; median (range) time on follow-up was 30.6 (0.6, 53.0) months and 31.4 (0.3, 52.5) months in each group, respectively.

Notes:

[31] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was pre-specified for Phase 3 participants only.

End point values	Phase 3: Placebo + Pembrolizumab	Phase 3: Talimogene Laherparepvec + Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	346	346		
Units: percentage of participants				
number (confidence interval 95%)	39.9 (34.72 to 45.04)	49.1 (43.87 to 54.40)		

Statistical analyses

Statistical analysis title	Analysis of iORR
Comparison groups	Phase 3: Placebo + Pembrolizumab v Phase 3: Talimogene Laherparepvec + Pembrolizumab
Number of subjects included in analysis	692
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.02 [32]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.44

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.06
upper limit	1.96

Notes:

[32] - Logistic regression stratified by randomization stratification factors (disease stage and prior BRAF inhibitor therapy) and the baseline PD-L1 status.

Secondary: Phase 3: Best Overall Response Assessed Using Modified irRC-RECIST

End point title	Phase 3: Best Overall Response Assessed Using Modified irRC-RECIST[33]

End point description:

Best overall response is defined as the best overall visit response in the following order: iCR, iPR, stable disease per modified irRC-RECIST (iSD), iPD, or UE per modified irRC-RECIST (iUE), evaluated by blinded independent central review.
iCR: Disappearance of all lesions and confirmation by a repeat, consecutive assessment at least 4 weeks from the date first documented. Any pathological lymph nodes must have reduction in short axis to <10 mm.
iPR: Decrease in tumor burden ≥ 30% relative to baseline confirmed by a consecutive assessment at least 4 weeks after first documentation.
iPD: Increase in tumor burden ≥ 20 % and at least 5 mm absolute increase relative to nadir confirmed by a repeat, consecutive assessment at least 4 weeks from the initial detection.
iSD: Neither sufficient shrinkage to qualify for iCR or iPR nor sufficient increase to qualify for iPD with ≥ 84 days elapsed after randomization.

End point type	Secondary

End point timeframe:

Tumor assessments were performed every 12 weeks after initiation of treatment until confirmed PD or start of new anticancer treatment; median (range) time on follow-up was 30.6 (0.6, 53.0) months and 31.4 (0.3, 52.5) months in each group, respectively.

Notes:

[33] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was pre-specified for Phase 3 participants only.

End point values	Phase 3: Placebo + Pembrolizumab	Phase 3: Talimogene Laherparepvec + Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	346	346		
Units: participants				
Complete response (iCR)	28	50		
Partial response (iPR)	110	120		
Stable disease (iSD)	57	51		
Progressive disease (iPD)	56	65		
Unevaluable (iUE)	69	30		
Not done	26	30		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 3: Durable Response Rate Assessed Using Modified irRC-RECIST (iDRR)

End point title	Phase 3: Durable Response Rate Assessed Using Modified irRC-RECIST (iDRR)[34]

End point description:

Durable response rate per modified irRC-RECIST is defined as the percentage of participants with a best overall response of iCR or iPR per modified irRC-RECIST evaluated by blinded independent central review with a duration of response ≥ 6 months.
iCR: Disappearance of all lesions (whether measurable or not and whether baseline or new) and confirmation by a repeat, consecutive assessment at least 4 weeks from the date first documented. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
iPR: Decrease in tumor burden ≥ 30% relative to baseline confirmed by a consecutive assessment at least 4 weeks after first documentation.

End point type	Secondary

End point timeframe:

Tumor assessments were performed every 12 weeks after initiation of treatment until confirmed PD or start of new anticancer treatment; median (range) time on follow-up was 30.6 (0.6, 53.0) months and 31.4 (0.3, 52.5) months in each group, respectively.

Notes:

[34] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was pre-specified for Phase 3 participants only.

End point values	Phase 3: Placebo + Pembrolizumab	Phase 3: Talimogene Laherparepvec + Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	346	346		
Units: percentage of participants				
number (confidence interval 95%)	34.4 (29.39 to 39.40)	45.7 (40.42 to 50.91)		

Statistical analyses

Statistical analysis title	Analysis of iDRR
Comparison groups	Phase 3: Placebo + Pembrolizumab v Phase 3: Talimogene Laherparepvec + Pembrolizumab
Number of subjects included in analysis	692
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.004 [35]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.16
upper limit	2.17

Notes:

[35] - Logistic regression stratified by randomization stratification factors (disease stage and prior BRAF inhibitor therapy) and the baseline PD-L1 status.

Secondary: Phase 3: Duration of Response Assessed Using Modified irRC-RECIST (iDOR)

End point title	Phase 3: Duration of Response Assessed Using Modified irRC-RECIST (iDOR)[36]

End point description:

Duration of response per modified irRC-RECIST is defined as the time from the date of an initial response of iCR or iPR that was subsequently confirmed to the earlier of iPD per modified irRC-RECIST evaluated by blinded independent central review, or death. Participants who had not ended their response at the time of analysis were censored at their last evaluable tumor assessment date before the start of the first subsequent anticancer therapy. "99999" indicates values that could not be estimated due to the low number of events.

End point type	Secondary

End point timeframe:

From randomization until the data cut-off date of 29 September 2020; median time on follow-up was 30.6 (0.6, 53.0) months in the Placebo + Pembrolizumab arm and 31.4 (0.3, 52.5) months in the Talimogene Laherparepvec + Pembrolizumab arm.

Notes:

[36] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was pre-specified for Phase 3 participants only.

End point values	Phase 3: Placebo + Pembrolizumab	Phase 3: Talimogene Laherparepvec + Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	138	170		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	43.7 (34.53 to 43.73)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 3: Disease Control Rate Assessed Using Modified irRC-RECIST (iDCR)

End point title	Phase 3: Disease Control Rate Assessed Using Modified irRC-RECIST (iDCR)[37]

End point description:

Disease control rate per modified irRC-RECIST is defined as the percentage of participants with a best overall response of iCR, iCR, or iSD assessed using modified irRC-RECIST evaluated by blinded independent central review.

iCR: Disappearance of all lesions (whether measurable or not and whether baseline or new) and confirmation by a repeat, consecutive assessment at least 4 weeks from the date first documented. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
iPR: Decrease in tumor burden ≥ 30% relative to baseline confirmed by a consecutive assessment at least 4 weeks after first documentation.
iSD: Neither sufficient shrinkage to qualify for iCR or iPR nor sufficient increase to qualify for iPD with ≥ 84 days elapsed after randomization.

End point type	Secondary

End point timeframe:

Tumor assessments were performed every 12 weeks after initiation of treatment until confirmed PD or start of new anticancer treatment; median (range) time on follow-up was 30.6 (0.6, 53.0) months and 31.4 (0.3, 52.5) months in each group, respectively.

Notes:

[37] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was pre-specified for Phase 3 participants only.

End point values	Phase 3: Placebo + Pembrolizumab	Phase 3: Talimogene Laherparepvec + Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	346	346		
Units: percentage of participants				
number (confidence interval 95%)	56.4 (51.13 to 61.58)	63.9 (58.81 to 68.93)		

Statistical analyses

Statistical analysis title	Analysis of iDCR
Comparison groups	Phase 3: Placebo + Pembrolizumab v Phase 3: Talimogene Laherparepvec + Pembrolizumab
Number of subjects included in analysis	692
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.058 [38]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.99
upper limit	1.85

Notes:

[38] - Logistic regression stratified by randomization stratification factors (disease stage and prior BRAF inhibitor therapy) and the baseline PD-L1 status.

Secondary: Phase 3: Change From Baseline in European Organisation for Research and Treatment of Cancer Quality of Life Core Module (EORTC QLQ-C30) Global Health Status (GHS)/Quality of Life (QOL) Score

End point title	Phase 3: Change From Baseline in European Organisation for Research and Treatment of Cancer Quality of Life Core Module (EORTC QLQ-C30) Global Health Status (GHS)/Quality of Life (QOL) Score[39]

End point description:

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) is a 30-question tool used to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status/quality of life scale, 5 functional scales, and 9 symptom scales/items.

The global health/QoL scale consists of 2 questions that ask participants to rate their overall health and overall quality of life during the past week on a scale from 1 (very poor) to 7 (excellent). The GHS/QoL subscale score was derived as the mean of each score then transformed to a scale from 0 to 100 where higher scores represent a better health status and a positive change from baseline indicates improvement.
The overall change from baseline (calculated from all on-treatment visits) was calculated using a restricted maximum likelihood-based mixed model for repeated measures (MMRM) (see model details in statistical analysis section).

End point type	Secondary

End point timeframe:

Baseline and day 1 of weeks 3, 6, 9, 12, then every 6 weeks until end of study treatment; median (range) duration of treatment was 39.0 (0.1, 107.3) weeks in Placebo + Pembrolizumab and 54.1 (0.1, 109.6) weeks in Talimogene Laherparepvec + Pembrolizumab.

Notes:

[39] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was pre-specified for Phase 3 participants only.

End point values	Phase 3: Placebo + Pembrolizumab	Phase 3: Talimogene Laherparepvec + Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	329[40]	328[41]		
Units: score on a scale				
least squares mean (standard error)	-0.20 (± 1.02)	-0.02 (± 1.02)		

Notes:

[40] - Participants who received at least 1 dose of study drug with baseline and ≥ 1 on-treatment value.

[41] - Participants who received at least 1 dose of study drug with baseline and ≥ 1 on-treatment value.

Statistical analyses

Statistical analysis title	Analysis of EORTC QLQ-C30 GHS/QOL

Statistical analysis description:

Mixed Model for Repeated Measures include the fixed and categorical effects of treatment, visit and treatment-by-visit interaction, the fixed and continuous covariates of baseline HRQL score, randomization stratification factors (stage of disease and prior BRAF inhibitor therapy per IVRS) and baseline PD-L1 status (positive and not positive). Random subject effect was modeled using within subject-error correlation structure.

Comparison groups	Phase 3: Placebo + Pembrolizumab v Phase 3: Talimogene Laherparepvec + Pembrolizumab
Number of subjects included in analysis	657
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.84
Method	Mixed Model for Repeated Measures
Parameter estimate	Difference
Point estimate	0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.67
upper limit	2.05
Variability estimate	Standard error of the mean
Dispersion value	0.95

Secondary: Number of Participants with Treatment-emergent Adverse Events (TEAEs)

End point title	Number of Participants with Treatment-emergent Adverse Events (TEAEs)

End point description:

An adverse event (AE) is any untoward medical occurrence in a clinical trial subject, including worsening of a pre-existing medical condition. The event does not necessarily have a causal relationship with study treatment. TEAEs include AEs from the first dose of study drug to 30 days after the last dose.
A serious adverse event (SAE) is an AE that met at least 1 of the following criteria:
-fatal;
-life threatening;
-required in-patient hospitalization or prolongation of existing hospitalization;
-resulted in persistent or significant disability/incapacity;
-congenital anomaly/birth defect;
-other medically important serious event.
Treatment-emergent SAEs are any SAE occurring from first dose of study drug through 90 days after the last dose or 30 days after the last dose if new anticancer therapy was started, whichever was earlier.
AEs were graded for severity using CTCAE V4.0, where Grade 1 = Mild; Grade 2 = Moderate; Grade 3 = Severe; Grade 4 = Life-threatening; Grade 5.

End point type	Secondary

End point timeframe:

From first dose to 30 days after last dose (90 days for SAEs); median (range) duration was 48 (5.1, 110.1) weeks in Phase 1b, 39 (0.1, 107.3) weeks in Placebo + Pembrolizumab and 56 (0.1, 109.6) weeks in Phase 3 Talimogene Laherparepvec + Pembrolizumab.

End point values	Phase 1b: Talimogene Laherparepvec + Pembrolizumab	Phase 3: Placebo + Pembrolizumab	Phase 3: Talimogene Laherparepvec + Pembrolizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21	344	344	
Units: participants				
Any treatment-emergent adverse events	21	331	338	
Grade ≥ 2	20	279	306	
Grade ≥ 3	13	151	161	
Grade ≥ 4	2	29	33	
Serious adverse events	8	141	154	
Leading to discontinuation of T-VEC/Placebo	0	24	26	
Leading to discontinuation of pembrolizumab	2	41	43	
Fatal adverse events	1	42	45	

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug to 30 days after last dose (90 days for SAEs); median (range) duration was 48 (5.1, 110) weeks in Phase 1b, 39 (0.1, 107) weeks in Placebo arm and 56 (0.1, 110) weeks in T-VEC arm. Deaths are reported up to the end of study.

Adverse event reporting additional description:

Adverse events are reported for all subjects who received at least 1 dose of T-VEC or pembrolizumab. One subject who was randomized in Phase 3 to receive placebo received T-VEC; thus the Safety Analysis Set consisted of 344 subjects in the talimogene laherparepvec + pembrolizumab group and 344 subjects in the placebo + pembrolizumab arm.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Phase 1b: Talimogene Laherparepvec + Pembrolizumab

Reporting group description:

Participants received talimogene laherparepvec at an initial dose of up to 4 mL 10 plaque-forming units (PFU)/mL by intralesional injection. Subsequent doses of talimogene laherparepvec at up to 4 mL of 10^8 PFU/mL began 3 weeks after the first dose and were administered every 2 weeks until disappearance of injectable lesions, complete response (CR), confirmed disease progression (PD) per modified Immune-related Response Criteria (irRC), intolerance of study treatment, 24 months from the date of the first dose of pembrolizumab, or end of study, whichever occurred first. Participants also received 200 mg pembrolizumab administered intravenously every 2 weeks starting at the time of the third dose of talimogene laherparepvec (week 6) until confirmed PD per modified irRC, treatment intolerance, 24 months from the first dose, or end of study, whichever occurred first.

Reporting group title	Phase 3: Placebo + Pembrolizumab

Reporting group description:

Participants received up to 4 mL placebo to talimogene laherparepvec by intralesional injection on day 1 of week 0. Subsequent doses of placebo (up to 4 mL) began 3 weeks after the first dose and were administered every 2 weeks until the fifth injection (week 9), and then synchronously with pembrolizumab thereafter every 3 weeks until disappearance of injectable lesions, complete response per modified Immune-related Response Criteria simulating Response Evaluation Criteria in Solid Tumors (irRC-RECIST) (iCR), confirmed iPD per modified irRC-RECIST, intolerance of study treatment, 24 months from the date of the first dose of placebo, or end of study, whichever occurred first. Participants also received 200 mg pembrolizumab administered intravenously every 3 weeks starting on day 1 of week 0, until confirmed iPD per modified irRC-RECIST, treatment intolerance, 24 months from the first dose, or end of study, whichever occurred first.

Reporting group title	Phase 3: Talimogene Laherparepvec + Pembrolizumab

Reporting group description:

Participants received talimogene laherparepvec at an initial dose of up to 4 mL 10 PFU/mL by intralesional injection on day 1. Subsequent doses of talimogene laherparepvec at 10^8 PFU/mL (up to 4 mL) began 3 weeks after the first dose and were administered every 2 weeks until the fifth injection of talimogene laherparepvec (week 9), and then synchronously with pembrolizumab thereafter every 3 weeks until disappearance of injectable lesions, iCR, confirmed iPD per modified irRC-RECIST, intolerance of study treatment, 24 months from the date of the first dose of talimogene laherparepvec, or end of study, whichever occurred first. Participants also received 200 mg pembrolizumab administered intravenously every 3 weeks starting on day 1 of week 0, until confirmed iPD per modified irRC-RECIST, treatment intolerance, 24 months from the first dose, or end of study, whichever occurred first.

Serious adverse events	Phase 1b: Talimogene Laherparepvec + Pembrolizumab	Phase 3: Placebo + Pembrolizumab	Phase 3: Talimogene Laherparepvec + Pembrolizumab
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 21 (38.10%)	141 / 344 (40.99%)	154 / 344 (44.77%)
number of deaths (all causes)	6	155	145
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma gastric			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma of colon			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Basal cell carcinoma			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder adenocarcinoma stage unspecified			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Endometrial cancer			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Intraductal proliferative breast lesion			

subjects affected / exposed	1 / 21 (4.76%)	0 / 344 (0.00%)	0 / 344 (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
Malignant melanoma			
subjects affected / exposed	0 / 21 (0.00%)	26 / 344 (7.56%)	27 / 344 (7.85%)
occurrences causally related to treatment / all	0 / 0	0 / 26	1 / 29
deaths causally related to treatment / all	0 / 0	0 / 19	0 / 20
Malignant neoplasm progression			
subjects affected / exposed	1 / 21 (4.76%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Melanoma recurrent			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Metastases to bone			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to central nervous system			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	3 / 344 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Metastases to lung			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to nervous system			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Metastatic malignant melanoma			

subjects affected / exposed	0 / 21 (0.00%)	10 / 344 (2.91%)	7 / 344 (2.03%)
occurrences causally related to treatment / all	0 / 0	0 / 11	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 8	0 / 5
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	2 / 344 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transitional cell carcinoma			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Tumour associated fever			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour haemorrhage			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	2 / 344 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Arteritis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			

subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Labile blood pressure			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Peripheral artery occlusion			
subjects affected / exposed	0 / 21 (0.00%)	2 / 344 (0.58%)	0 / 344 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subclavian vein thrombosis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombophlebitis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Vena cava thrombosis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Axillary lymphadenectomy			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	0 / 21 (0.00%)	2 / 344 (0.58%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chills			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Condition aggravated			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Death			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	2 / 344 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Disease progression			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Fatigue			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	3 / 344 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	1 / 21 (4.76%)	2 / 344 (0.58%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Generalised oedema			

subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inflammation			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	2 / 344 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza like illness			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 21 (0.00%)	2 / 344 (0.58%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 1
Pain			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Performance status decreased			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	2 / 21 (9.52%)	4 / 344 (1.16%)	7 / 344 (2.03%)
occurrences causally related to treatment / all	0 / 2	2 / 4	6 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Swelling			

subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Cytokine release syndrome			
subjects affected / exposed	1 / 21 (4.76%)	0 / 344 (0.00%)	0 / 344 (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
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gynaecomastia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	2 / 344 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 21 (0.00%)	3 / 344 (0.87%)	5 / 344 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 3	1 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Immune-mediated pneumonitis			

subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Interstitial lung disease			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Lung infiltration			
subjects affected / exposed	1 / 21 (4.76%)	0 / 344 (0.00%)	0 / 344 (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
Pleural effusion			
subjects affected / exposed	0 / 21 (0.00%)	2 / 344 (0.58%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pneumonitis			
subjects affected / exposed	1 / 21 (4.76%)	4 / 344 (1.16%)	5 / 344 (1.45%)
occurrences causally related to treatment / all	1 / 1	4 / 4	6 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax spontaneous			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	2 / 344 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pulmonary sarcoidosis			

subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 21 (0.00%)	2 / 344 (0.58%)	3 / 344 (0.87%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 3
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 1
Sleep apnoea syndrome			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Confusional state			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Delirium			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Mental status changes			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obsessive-compulsive disorder			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Somatic symptom disorder			

subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical condition abnormal			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Injury, poisoning and procedural complications			
Bone contusion			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Contusion			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Fall			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	2 / 344 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	3 / 344 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hip fracture			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Humerus fracture			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion related reaction			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar vertebral fracture			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple fractures			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Overdose			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Pseudomeningocele			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Skin laceration			

subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Spinal compression fracture			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	2 / 344 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Synovial rupture			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Toxicity to various agents			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Traumatic arthritis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Upper limb fracture			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 21 (0.00%)	2 / 344 (0.58%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute coronary syndrome			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Angina pectoris			

subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 21 (0.00%)	2 / 344 (0.58%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block second degree			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Cardiac failure			
subjects affected / exposed	0 / 21 (0.00%)	2 / 344 (0.58%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiac failure acute			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiogenic shock			

subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Left ventricular failure			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Mitral valve prolapse			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 21 (0.00%)	3 / 344 (0.87%)	4 / 344 (1.16%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Myocarditis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Supraventricular tachycardia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Basal ganglia infarction			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Carotid artery stenosis			

subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Central nervous system necrosis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Dementia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Dizziness			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	2 / 344 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolic stroke			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial paralysis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Headache			

subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Hydrocephalus			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic cerebral infarction			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Ischaemic stroke			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Migraine			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Nervous system disorder			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neurological symptom			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Paraesthesia			

subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Paraparesis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Paraplegia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Seizure			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Speech disorder			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Spinal cord compression			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Syncope			
subjects affected / exposed	0 / 21 (0.00%)	2 / 344 (0.58%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	0 / 21 (0.00%)	8 / 344 (2.33%)	9 / 344 (2.62%)
occurrences causally related to treatment / all	0 / 0	1 / 17	1 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia of malignant disease			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Lymph node pain			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Granulomatous lymphadenitis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Lymphadenopathy			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	2 / 344 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 21 (0.00%)	2 / 344 (0.58%)	0 / 344 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	2 / 344 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			

Papilloedema			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal oedema			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uveitis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	2 / 344 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 21 (0.00%)	2 / 344 (0.58%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune colitis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Colitis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	5 / 344 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	5 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			

subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	2 / 344 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	4 / 344 (1.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematochezia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoperitoneum			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Large intestine polyp			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mechanical ileus			

subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Nausea			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	2 / 344 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal motility disorder			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	1 / 21 (4.76%)	1 / 344 (0.29%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	1 / 21 (4.76%)	1 / 344 (0.29%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cholecystitis acute			

subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Cholelithiasis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Hepatic failure			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hepatitis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	2 / 344 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dermatitis bullous			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Drug eruption			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Eczema			

subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Skin hypopigmentation			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
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 lesion			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Skin ulcer			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stevens-Johnson syndrome			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	2 / 344 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrotic syndrome			

subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Renal colic			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Renal failure			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Renal impairment			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Ureteric obstruction			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Addison's disease			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Adrenal insufficiency			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Adrenocortical insufficiency acute			

subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Endocrine disorder			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Hyperthyroidism			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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 / 21 (0.00%)	2 / 344 (0.58%)	0 / 344 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypopituitarism			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphocytic hypophysitis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	2 / 344 (0.58%)
occurrences causally related to treatment / all	0 / 0	1 / 1	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroid mass			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroiditis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthropathy			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Back pain			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	2 / 344 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc degeneration			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Intervertebral disc protrusion			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	2 / 344 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint effusion			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar spinal stenosis			
subjects affected / exposed	1 / 21 (4.76%)	0 / 344 (0.00%)	0 / 344 (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
Myositis			

subjects affected / exposed	0 / 21 (0.00%)	3 / 344 (0.87%)	0 / 344 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Pain in extremity			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pathological fracture			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	2 / 344 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polyarthritis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psoriatic arthropathy			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal pain			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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			
Abscess			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Anal abscess			

subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Appendicitis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Atypical pneumonia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Bronchitis			
subjects affected / exposed	0 / 21 (0.00%)	2 / 344 (0.58%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 21 (4.76%)	0 / 344 (0.00%)	0 / 344 (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
Cellulitis			
subjects affected / exposed	1 / 21 (4.76%)	4 / 344 (1.16%)	4 / 344 (1.16%)
occurrences causally related to treatment / all	0 / 1	2 / 4	1 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chorioretinitis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dermo-hypodermitis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			

subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Encephalitis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 21 (0.00%)	2 / 344 (0.58%)	2 / 344 (0.58%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia sepsis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extradural abscess			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Infected cyst			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Infection			

subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised infection			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Lower respiratory tract infection			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymph gland infection			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis aseptic			
subjects affected / exposed	1 / 21 (4.76%)	0 / 344 (0.00%)	0 / 344 (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
Nasopharyngitis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Periorbital cellulitis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	0 / 21 (0.00%)	4 / 344 (1.16%)	3 / 344 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 4	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary sepsis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Postoperative wound infection			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis chronic			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Scrotal abscess			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth abscess			

subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheobronchitis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Upper respiratory tract infection			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteritis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Urinary tract infection			
subjects affected / exposed	0 / 21 (0.00%)	3 / 344 (0.87%)	5 / 344 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection bacterial			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Wound infection			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	2 / 344 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Dehydration			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	3 / 344 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	2 / 344 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Hyperglycaemia			
subjects affected / exposed	0 / 21 (0.00%)	2 / 344 (0.58%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Hyponatraemia			
subjects affected / exposed	0 / 21 (0.00%)	3 / 344 (0.87%)	2 / 344 (0.58%)
occurrences causally related to treatment / all	0 / 0	2 / 3	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour lysis syndrome			

subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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
Type 1 diabetes mellitus			
subjects affected / exposed	0 / 21 (0.00%)	0 / 344 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 21 (0.00%)	1 / 344 (0.29%)	0 / 344 (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

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

Non-serious adverse events	Phase 1b: Talimogene Laherparepvec + Pembrolizumab	Phase 3: Placebo + Pembrolizumab	Phase 3: Talimogene Laherparepvec + Pembrolizumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 21 (100.00%)	305 / 344 (88.66%)	317 / 344 (92.15%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma			
subjects affected / exposed	3 / 21 (14.29%)	1 / 344 (0.29%)	1 / 344 (0.29%)
occurrences (all)	3	2	1
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 21 (4.76%)	22 / 344 (6.40%)	19 / 344 (5.52%)
occurrences (all)	1	36	36
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 21 (9.52%)	29 / 344 (8.43%)	27 / 344 (7.85%)
occurrences (all)	2	38	33
Chills			
subjects affected / exposed	8 / 21 (38.10%)	17 / 344 (4.94%)	73 / 344 (21.22%)
occurrences (all)	14	19	153
Face oedema			

subjects affected / exposed	2 / 21 (9.52%)	0 / 344 (0.00%)	3 / 344 (0.87%)
occurrences (all)	3	0	3
Fatigue			
subjects affected / exposed	15 / 21 (71.43%)	94 / 344 (27.33%)	137 / 344 (39.83%)
occurrences (all)	25	128	214
Influenza like illness			
subjects affected / exposed	5 / 21 (23.81%)	26 / 344 (7.56%)	64 / 344 (18.60%)
occurrences (all)	10	35	143
Injection site pain			
subjects affected / exposed	2 / 21 (9.52%)	14 / 344 (4.07%)	15 / 344 (4.36%)
occurrences (all)	2	24	20
Injection site reaction			
subjects affected / exposed	2 / 21 (9.52%)	3 / 344 (0.87%)	10 / 344 (2.91%)
occurrences (all)	4	3	14
Oedema peripheral			
subjects affected / exposed	5 / 21 (23.81%)	22 / 344 (6.40%)	27 / 344 (7.85%)
occurrences (all)	8	23	35
Pain			
subjects affected / exposed	1 / 21 (4.76%)	18 / 344 (5.23%)	24 / 344 (6.98%)
occurrences (all)	2	23	33
Pyrexia			
subjects affected / exposed	10 / 21 (47.62%)	33 / 344 (9.59%)	128 / 344 (37.21%)
occurrences (all)	29	46	352
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 21 (38.10%)	44 / 344 (12.79%)	58 / 344 (16.86%)
occurrences (all)	8	49	72
Dyspnoea			
subjects affected / exposed	4 / 21 (19.05%)	24 / 344 (6.98%)	23 / 344 (6.69%)
occurrences (all)	4	26	37
Pneumonitis			
subjects affected / exposed	2 / 21 (9.52%)	7 / 344 (2.03%)	18 / 344 (5.23%)
occurrences (all)	2	11	28
Psychiatric disorders			

Anxiety			
subjects affected / exposed	2 / 21 (9.52%)	7 / 344 (2.03%)	11 / 344 (3.20%)
occurrences (all)	2	7	13
Insomnia			
subjects affected / exposed	3 / 21 (14.29%)	27 / 344 (7.85%)	23 / 344 (6.69%)
occurrences (all)	5	29	27
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 21 (14.29%)	23 / 344 (6.69%)	26 / 344 (7.56%)
occurrences (all)	6	34	35
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 21 (14.29%)	16 / 344 (4.65%)	20 / 344 (5.81%)
occurrences (all)	3	25	29
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 21 (9.52%)	7 / 344 (2.03%)	15 / 344 (4.36%)
occurrences (all)	3	9	19
Blood iron decreased			
subjects affected / exposed	2 / 21 (9.52%)	1 / 344 (0.29%)	0 / 344 (0.00%)
occurrences (all)	2	1	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 21 (9.52%)	3 / 344 (0.87%)	4 / 344 (1.16%)
occurrences (all)	2	4	4
Infusion related reaction			
subjects affected / exposed	2 / 21 (9.52%)	0 / 344 (0.00%)	4 / 344 (1.16%)
occurrences (all)	2	0	7
Procedural pain			
subjects affected / exposed	2 / 21 (9.52%)	5 / 344 (1.45%)	9 / 344 (2.62%)
occurrences (all)	2	5	9
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 21 (42.86%)	44 / 344 (12.79%)	62 / 344 (18.02%)
occurrences (all)	13	59	144
Neuropathy peripheral			
subjects affected / exposed	2 / 21 (9.52%)	0 / 344 (0.00%)	4 / 344 (1.16%)
occurrences (all)	2	0	5

Paraesthesia			
subjects affected / exposed	2 / 21 (9.52%)	6 / 344 (1.74%)	13 / 344 (3.78%)
occurrences (all)	3	7	13
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 21 (9.52%)	26 / 344 (7.56%)	33 / 344 (9.59%)
occurrences (all)	6	45	46
Leukopenia			
subjects affected / exposed	2 / 21 (9.52%)	2 / 344 (0.58%)	0 / 344 (0.00%)
occurrences (all)	2	4	0
Eye disorders			
Visual impairment			
subjects affected / exposed	2 / 21 (9.52%)	2 / 344 (0.58%)	6 / 344 (1.74%)
occurrences (all)	2	2	7
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 21 (9.52%)	24 / 344 (6.98%)	23 / 344 (6.69%)
occurrences (all)	2	26	29
Abdominal pain upper			
subjects affected / exposed	2 / 21 (9.52%)	12 / 344 (3.49%)	7 / 344 (2.03%)
occurrences (all)	2	14	8
Constipation			
subjects affected / exposed	4 / 21 (19.05%)	28 / 344 (8.14%)	52 / 344 (15.12%)
occurrences (all)	5	36	63
Diarrhoea			
subjects affected / exposed	13 / 21 (61.90%)	73 / 344 (21.22%)	70 / 344 (20.35%)
occurrences (all)	17	124	118
Dry mouth			
subjects affected / exposed	1 / 21 (4.76%)	19 / 344 (5.52%)	14 / 344 (4.07%)
occurrences (all)	1	21	16
Frequent bowel movements			
subjects affected / exposed	2 / 21 (9.52%)	1 / 344 (0.29%)	0 / 344 (0.00%)
occurrences (all)	2	1	0
Nausea			
subjects affected / exposed	7 / 21 (33.33%)	61 / 344 (17.73%)	92 / 344 (26.74%)
occurrences (all)	10	78	123
Vomiting			

subjects affected / exposed	7 / 21 (33.33%)	29 / 344 (8.43%)	56 / 344 (16.28%)
occurrences (all)	8	35	86
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	2 / 21 (9.52%)	4 / 344 (1.16%)	6 / 344 (1.74%)
occurrences (all)	4	6	6
Alopecia			
subjects affected / exposed	3 / 21 (14.29%)	3 / 344 (0.87%)	10 / 344 (2.91%)
occurrences (all)	3	3	11
Erythema			
subjects affected / exposed	2 / 21 (9.52%)	15 / 344 (4.36%)	15 / 344 (4.36%)
occurrences (all)	2	15	19
Pruritus			
subjects affected / exposed	7 / 21 (33.33%)	55 / 344 (15.99%)	61 / 344 (17.73%)
occurrences (all)	9	67	74
Rash			
subjects affected / exposed	9 / 21 (42.86%)	42 / 344 (12.21%)	61 / 344 (17.73%)
occurrences (all)	16	56	99
Rash erythematous			
subjects affected / exposed	2 / 21 (9.52%)	1 / 344 (0.29%)	4 / 344 (1.16%)
occurrences (all)	12	1	4
Rash macular			
subjects affected / exposed	2 / 21 (9.52%)	1 / 344 (0.29%)	6 / 344 (1.74%)
occurrences (all)	7	1	7
Rash maculo-papular			
subjects affected / exposed	3 / 21 (14.29%)	17 / 344 (4.94%)	20 / 344 (5.81%)
occurrences (all)	3	23	29
Skin lesion			
subjects affected / exposed	2 / 21 (9.52%)	2 / 344 (0.58%)	11 / 344 (3.20%)
occurrences (all)	2	2	13
Skin mass			
subjects affected / exposed	2 / 21 (9.52%)	2 / 344 (0.58%)	0 / 344 (0.00%)
occurrences (all)	4	2	0
Urticaria			
subjects affected / exposed	2 / 21 (9.52%)	2 / 344 (0.58%)	3 / 344 (0.87%)
occurrences (all)	2	3	3

Vitiligo			
subjects affected / exposed	5 / 21 (23.81%)	32 / 344 (9.30%)	44 / 344 (12.79%)
occurrences (all)	5	32	47
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	3 / 21 (14.29%)	20 / 344 (5.81%)	22 / 344 (6.40%)
occurrences (all)	3	20	22
Hypothyroidism			
subjects affected / exposed	6 / 21 (28.57%)	49 / 344 (14.24%)	48 / 344 (13.95%)
occurrences (all)	10	61	60
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	8 / 21 (38.10%)	66 / 344 (19.19%)	82 / 344 (23.84%)
occurrences (all)	16	93	140
Back pain			
subjects affected / exposed	3 / 21 (14.29%)	30 / 344 (8.72%)	35 / 344 (10.17%)
occurrences (all)	6	39	40
Muscle spasms			
subjects affected / exposed	2 / 21 (9.52%)	5 / 344 (1.45%)	9 / 344 (2.62%)
occurrences (all)	2	6	10
Myalgia			
subjects affected / exposed	2 / 21 (9.52%)	16 / 344 (4.65%)	33 / 344 (9.59%)
occurrences (all)	2	22	46
Pain in extremity			
subjects affected / exposed	4 / 21 (19.05%)	21 / 344 (6.10%)	29 / 344 (8.43%)
occurrences (all)	5	26	37
Infections and infestations			
Cellulitis			
subjects affected / exposed	2 / 21 (9.52%)	9 / 344 (2.62%)	14 / 344 (4.07%)
occurrences (all)	2	12	19
Influenza			
subjects affected / exposed	2 / 21 (9.52%)	7 / 344 (2.03%)	9 / 344 (2.62%)
occurrences (all)	2	9	9
Oral herpes			
subjects affected / exposed	2 / 21 (9.52%)	16 / 344 (4.65%)	15 / 344 (4.36%)
occurrences (all)	2	16	20

Nasopharyngitis			
subjects affected / exposed	1 / 21 (4.76%)	23 / 344 (6.69%)	21 / 344 (6.10%)
occurrences (all)	1	27	26
Rhinitis			
subjects affected / exposed	2 / 21 (9.52%)	11 / 344 (3.20%)	7 / 344 (2.03%)
occurrences (all)	2	12	8
Upper respiratory tract infection			
subjects affected / exposed	2 / 21 (9.52%)	17 / 344 (4.94%)	17 / 344 (4.94%)
occurrences (all)	3	20	20
Urinary tract infection			
subjects affected / exposed	1 / 21 (4.76%)	17 / 344 (4.94%)	22 / 344 (6.40%)
occurrences (all)	1	22	30
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 21 (0.00%)	26 / 344 (7.56%)	43 / 344 (12.50%)
occurrences (all)	0	29	53
Hyperglycaemia			
subjects affected / exposed	3 / 21 (14.29%)	11 / 344 (3.20%)	19 / 344 (5.52%)
occurrences (all)	11	16	60
Hyperkalaemia			
subjects affected / exposed	2 / 21 (9.52%)	5 / 344 (1.45%)	2 / 344 (0.58%)
occurrences (all)	2	6	2
Hypophosphataemia			
subjects affected / exposed	2 / 21 (9.52%)	3 / 344 (0.87%)	14 / 344 (4.07%)
occurrences (all)	3	9	18

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 May 2015	•Changed the Phase 2 part to Phase 3 •Included 2 Phase 3 primary endpoints, PFS and OS. The primary analysis of PFS will be based on tumor evaluation by a blinded independent central review (BICR) using RECIST 1.1 with modifications: 1) increased total target lesions to maximum of 10 (max 5 per organ), 2) new skin lesions will be considered in the overall non-target lesion assessment but will not automatically result in a response of PD. •Removed cross-over combination treatment. •Increased sample size of Phase 3 to 660 subjects for formal testing of PFS and OS. •Revised Phase 3 treatment schedule. •Updated Phase 3 prior therapy inclusion criteria. •Use irRC-RECIST for Phase 3 treatment decisions and secondary endpoints. •Added an event-driven analysis of the secondary PFS endpoint based on irRC-RECIST. •Updated Phase 3 measurable disease and tumor sample inclusion criteria. •Skin photographs and radiographs in Phase 3 will be submitted to BICR for evaluation of PFS and secondary response-related endpoints. •Removed option for retreatment. •Added Phase 1b re-analysis time points. •Added 2 interim safety, 1 interim ORR futility, 1 interim efficacy, and 1 interim analysis for OS in Phase 3. •Utilized an independent, external DMC in phase 3 to monitor safety and evaluate futility. •Updated the pembrolizumab-related pneumonitis toxicity management guidelines. •Updated tumor sample collection schedule in Phase 3. •Revised the schedule of safety laboratory assessments. •Secondary objectives of anti-pembrolizumab antibodies, pembrolizumab PK and changes in PD-L1 changed to exploratory objectives. •Ordinal categorical response score and deep response rate endpoints removed. •Moved evaluation of PRO in phase 3 from exploratory to secondary objective. •Clarified the responsibilities of the DLRT in Phase 1b. •Increased follow-up to 60 months after last subject enrolled. •Changed reporting period for pembrolizumab Events of Clinical Interest and the reporting period for SAEs.

25 September 2015	•Changed Phase 3 part to be double-blind and added placebo to the pembrolizumab arm. •Reordered sections to separate Phase 1b and Phase 3 throughout. •Updated background information for T-VEC and pembrolizumab to reflect recent data. •Added results of the completed dose level review team (DLRT) evaluation for Phase 1b. •Allowed for more flexibility in frequency of radiographic follow-up for subjects who have reached a confirmed clinical response (CR) in long term follow-up. •Updated contraception language for exclusion criterion and sections related to pembrolizumab. •Shortened period from ending prior adjuvant therapy to 28 days prior to enrollment. •Prior ipilimumab as adjuvant therapy is now allowed. •Added exclusion criteria for allogeneic hematopoietic stem cell transplantation and active tuberculosis. •Updated text related to pembrolizumab events of clinical interest, rescue medications, dose adjustment, overdose, and supportive care guidelines. Immune-related AEs are no longer considered pembrolizumab events of interest. •Combined the schedule of assessments tables for Phase 3 arms 1 and 2. •Injectable investigational product-related AEs during long-term follow-up will be collected. •Updated pregnancy and lactation reporting language. •Updated text for interim analysis and interim ORR futility analysis in Phase 3. If futility is declared on ORR, DCR will also need to have futility declared. This is to prevent the study treatment being declared futile when the ORR may not be adequately improved but the DCR is at the time of the interim analysis. •Updated text pertaining to the analysis for the secondary endpoint of PFS per irRC-RECIST (phase 3) and included text regarding multiplicity adjustment for clarification. •Removed RECIST 1.1 modification that new skin lesions will be considered in the overall non-target lesion assessment but will not automatically result in esponse of PD. •Updated language to clarify the modified response criteria in the appendices.
12 April 2017	•An event-driven overall survival interim analysis at 282 events (including futility analysis) added to the planned analyses in order to evaluate the efficacy/futility with approximately 70% power of the combination treatment at an earlier time point in order to facilitate regulatory submission if the combination demonstrates significant improvement in overall survival or stopping the study for futility in overall survival. •The interim futility analysis based on overall response rate and disease control rate for the data monitoring committee review was changed from the investigator assessment to a blinded independent central review. Using blinded independent central review assessed responses would provide a robust and consistent assessment of overall response rate and disease control rate as for the primary endpoint of progression free survival, which also utilizes blinded independent central review. The Bayesian priors for the combination arm were also revised to reflect new data available from the phase 1b part of the study. •The fallback procedure to test overall survival and progression free survival dual primaries with the Maurer-Bretz multiple testing procedure was revised. •The secondary objectives were updated to test additional hypotheses per modified irRC-RECIST by blinded independent central review, and overall survival excluding stage IVM1c. •The secondary and exploratory objectives related to patient reported outcomes were updated.

24 January 2018	•Replace the Dose Modification Guidelines for Pembrolizumab Related Adverse Events Table with the Pembrolizumab-related Adverse Event Management table to incorporate the new myocarditis risk and management and remove redundant and outdated information about management of pembrolizumab-related AEs. •Update the information and table regarding management of pembrolizumab-related infusion reactions. •Add thyroid testing up to 3 days before dosing and that study treatment can be administered before the results are reported if the subject is asymptomatic. •Clarify the response evaluation criteria used for Phase 1b and Phase 3 endpoints and update the matrix for determining overall response at each assessment. •Clarify the collection of archival biopsy. •Clarify when subjects should undergo safety follow-up procedures. •Allow survival status to be assessed at additional time points not specified in the Schedule of Assessments. •Clarify that for subjects with PD QLQ-C30 is not collected in long-term follow-up; however, EQ-5D-3L will be collected. •Clarify the timing of the beginning of the registry protocol; update the primary completion and end of trial dates. •Update T-VEC and pembrolizumab background information and the rationale for combination therapy. •Clarify timing of safety monitoring by the DMC. •Clarify that both clinical and photographic evaluations must be done for lesions which cannot be evaluated by radiographic imaging. •Clarify that prior tumor vaccines are allowable if administered in the adjuvant setting. •Clarify that subjects should return to the clinic within 3 days after notification of a suspected herpetic lesion. •Clarify that photographs of all visible lesions must be done at baseline to allow for follow-up of lesions during treatment. •Clarify that laboratory assessment up to 3 days prior to administration of study treatment is allowed. •Clarify the PRO analysis set. •Clarify the futility analysis of OS for a non-constant treatment effect.
15 January 2020	• Update statistical characteristics of the group sequential OS analyses and add a third interim OS analysis planned after 315 events. To optimize the opportunity to observe statistical significance prior to the OS primary analysis (PA) if there is a late survival effect that would not be achieved at OS interim analysis (IA)1 or OS IA2, an additional look at OS IA3 (n = 315) was added prior to the OS PA. The trigger for 315 was selected to achieve approximately half the information gain between n = 282 and n = 346, and is halfway between the expected timings of OS IA2 and OS PA. The protocol is amended to include this additional analysis prior to any formal evaluation of efficacy related to PFS or OS. Appropriate alpha was allocated for all of the efficacy analyses. • Update the background to include the updated OS results from the KEYNOTE-006 and CHECKMATE-067 trials. •Update exploratory objectives to evaluate PROs as assessed by the EORTC QLQ-C30 and EuroQoL-5D-3L (EQ-5D-3L) subscales and add language for PRO population assessment. • An exploratory endpoint assessing lesion level response was added. • Clarify covariates for efficacy in subgroup or multivariate analyses. • Clarify language for interim efficacy analyses including possible hypotheses tests at planned analyses and operating characteristics of the primary analysis of PFS and sequential tests of OS. • Add text to clarify that in the Phase 1b part when nodal disease regresses to below 10 mm, the nodal lesion measurement should be recorded as 0 x 0 mm instead of the actual measurement. • Clarify that no index lesions identified at baseline is associated with "Not applicable (NA)" instead of "Not done" in the matrix for determining overall response. Add "unevaluable (UE) or iUE (unevaluable by modified irRC-RECIST) to the matrix for determining overall response. • Clarify number of days after the date of enrollment for visit response of stable disease by modified irRC-RECIST (iSD) or better.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported