Clinical trial results:
A Randomized Phase 3 Clinical Trial to Evaluate the Efficacy and Safety of Treatment with OncoVEX^GM-CSF Compared to Subcutaneously Administered GM-CSF in Melanoma Patients with Unresectable Stage IIIb, IIIc and IV Disease

Summary

EudraCT number	2008-006140-20
Trial protocol	GB
Global end of trial date	08 August 2014

Results information

Result version number	v1 (current)
This version publication date	21 May 2016
First version publication date	21 May 2016

Trial information

Trial identification

Sponsor protocol code	005/05

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00769704
WHO universal trial number (UTN)	-
Other trial identifiers	20110263: Amgen study ID

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)	
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 August 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 August 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this study is to evaluate the efficacy and safety of treatment with talimogene laherparepvec compared to subcutaneously administered GM-CSF in patients with unresectable Stage IIIb, IIIc and Stage IV melanoma. The efficacy endpoints of the study aim to demonstrate overall clinical benefit for patients treated with talimogene laherparepvec as compared to GM-CSF.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines.
Written informed consent, properly witnessed and executed, was obtained from each subject before study entry.
The protocol, informed consent, and other appropriate study documentation were approved by the Independent Ethics Committee (IEC) or Institutional Review Board (IRB) of each study center before the study began.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 April 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	36 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	South Africa: 14
Country: Number of subjects enrolled	United Kingdom: 33
Country: Number of subjects enrolled	United States: 383
Worldwide total number of subjects	437
EEA total number of subjects	33

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)	225
From 65 to 84 years	191
85 years and over	21

Subject disposition

Recruitment

Recruitment details:

Eligible patients were adults with histologically confirmed, not surgically resectable, stage IIIB - IV melanoma suitable for direct or ultrasound-guided injection.
Among those randomized, the first patient enrolled 29 April 2009 and last patient enrolled 8 June 2011.
1 patient randomized 3 times is counted once under talimogene laherparepvec.

Pre-assignment

Screening details:

Patients were assigned at a 2:1 ratio using central random assignment to receive intralesional talimogene laherparepvec or subcutaneous granulocyte macrophage colony-stimulating factor (GM-CSF). Randomization was stratified by site of first recurrence, presence of liver metastases, disease stage, and prior nonadjuvant systemic treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	GM-CSF

Arm description:

Granulocyte macrophage colony-stimulating factor (GM-CSF) was administered at a dose of 125 µg/m²/day subcutaneously for 14 days in 28-day cycles for 24 weeks. Participants could continue treatment until clinically relevant disease progression, intolerability, withdrawal of consent, complete remission, or lack of response by 12 months, for a maximum of 18 months.

Arm type	Active comparator
Investigational medicinal product name	GM-CSF
Investigational medicinal product code	
Other name	Leukine, Sargramostim
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

125 µg/m² subcutaneous injection

Arm title	Talimogene Laherparepvec

Arm description:

Participants received talimogene laherparepvec on Days 1 and 15 of each 28-day cycle for 24 weeks. The initial dose of talimogene laherparepvec was at a concentration of 10^6 plaque forming units (PFU)/mL, injected into 1 or more skin, subcutaneous or nodal tumors. Subsequent doses began at least 3 weeks after the first dose and consisted of talimogene laherparepvec at a concentration of 10^8 PFU/mL. Participants could continue treatment until clinically relevant disease progression, intolerability, withdrawal of consent, complete remission, lack of response by 12 months, or disappearance of all injectable lesions, for a maximum of 18 months.

Arm type	Experimental
Investigational medicinal product name	Talimogene laherparepvec
Investigational medicinal product code	
Other name	OncoVEX^GM-CSF, IMLYGIC™
Pharmaceutical forms	Solution for injection
Routes of administration	Intratumoral use

Dosage and administration details:

Up to 4 mL of 10^8 pfu/mL/per intratumoral injection

Number of subjects in period 1	GM-CSF	Talimogene Laherparepvec
Started	141	296
Intent-to-treat Population	141	295
Received Treatment	127	292
Completed	30	97
Not completed	111	199
Consent withdrawn by subject	12	5
Death	95	190
Other	1	2
Lost to follow-up	3	2

Baseline characteristics

Reporting groups	
Reporting group title	GM-CSF
Reporting group description:	
Granulocyte macrophage colony-stimulating factor (GM-CSF) was administered at a dose of 125 µg/m²/day subcutaneously for 14 days in 28-day cycles for 24 weeks. Participants could continue treatment until clinically relevant disease progression, intolerability, withdrawal of consent, complete remission, or lack of response by 12 months, for a maximum of 18 months.	
Reporting group title	Talimogene Laherparepvec
Reporting group description:	
Participants received talimogene laherparepvec on Days 1 and 15 of each 28-day cycle for 24 weeks. The initial dose of talimogene laherparepvec was at a concentration of 10^6 plaque forming units (PFU)/mL, injected into 1 or more skin, subcutaneous or nodal tumors. Subsequent doses began at least 3 weeks after the first dose and consisted of talimogene laherparepvec at a concentration of 10^8 PFU/mL. Participants could continue treatment until clinically relevant disease progression, intolerability, withdrawal of consent, complete remission, lack of response by 12 months, or disappearance of all injectable lesions, for a maximum of 18 months.	

Reporting group values	GM-CSF	Talimogene Laherparepvec	Total
Number of subjects	141	296	437
Age categorical Units: Subjects			
Adults (18-64 years)	72	153	225
From 65-84 years	63	128	191
85 years and over	6	15	21
Age Continuous Units: years			
arithmetic mean	62.92	63.07	
standard deviation	± 14.13	± 13.68	-
Gender, Male/Female Units: participants			
Female	64	123	187
Male	77	173	250
Race/Ethnicity, Customized Units: Subjects			
White	138	290	428
Black	2	1	3
Asian	0	1	1
Native Hawaiian or Other Pacific Islander	0	1	1
Other	1	3	4
Eastern Cooperative Oncology Group (ECOG) Performance Status			
Scale used to assess how a patient's disease is progressing, how the disease affects the daily living abilities of the patient: 0 = Fully active, able to carry on all pre-disease performance without restriction; 1 = Restricted in physically strenuous activity, ambulatory, able to carry out work of a light nature; 2 = Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about > 50% of waking hours; 3 = Capable of only limited self care, confined to a bed or chair > 50% of waking hours; 4 = Completely disabled, confined to bed or chair; 5 = Dead.			
Units: Subjects			
Grade 0	97	210	307
Grade 1	32	82	114

Missing	12	4	16
Tumor, Node, Metastasis (TNM) Disease Stage			
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	12	22	34
Stage IIIC	31	66	97
Stage IV M1a	43	76	119
Stage IV M1b	26	64	90
Stage IV M1c	29	67	96
Missing	0	1	1
Line of Therapy Units: Subjects			
First Line	65	138	203
Second Line or Greater	76	158	234

End points

End points reporting groups

Reporting group title	GM-CSF

Reporting group description:

Granulocyte macrophage colony-stimulating factor (GM-CSF) was administered at a dose of 125 µg/m²/day subcutaneously for 14 days in 28-day cycles for 24 weeks. Participants could continue treatment until clinically relevant disease progression, intolerability, withdrawal of consent, complete remission, or lack of response by 12 months, for a maximum of 18 months.

Reporting group title	Talimogene Laherparepvec

Reporting group description:

Participants received talimogene laherparepvec on Days 1 and 15 of each 28-day cycle for 24 weeks. The initial dose of talimogene laherparepvec was at a concentration of 10^6 plaque forming units (PFU)/mL, injected into 1 or more skin, subcutaneous or nodal tumors. Subsequent doses began at least 3 weeks after the first dose and consisted of talimogene laherparepvec at a concentration of 10^8 PFU/mL. Participants could continue treatment until clinically relevant disease progression, intolerability, withdrawal of consent, complete remission, lack of response by 12 months, or disappearance of all injectable lesions, for a maximum of 18 months.

Primary: Durable Response Rate

End point title	Durable Response Rate

End point description:

Durable response rate was defined as the percentage of participants with a complete response (CR) or partial response (PR) maintained continuously for at least 6 months from the time the objective response was first observed and initiating within 12 months of starting therapy as assessed by the Endpoint Assessment Committee (EAC). This reflects all new sites of disease as well as disease sites identified at baseline.
Disease assessments were performed at the beginning of each treatment cycle in accordance with modified World Health Organization criteria.
CR: Disappearance of all clinical evidence of tumor (both measurable and non-measurable but evaluable disease);
PR: ≥ 50% reduction in the sum of the products of the perpendicular diameters of all measurable tumors at the time of assessment as compared to baseline.
The intent-to-treat population included all participants randomized to receive study treatment, excluding one participant who was randomized three times.

End point type	Primary

End point timeframe:

From randomization until the data cut-off date of 21 December 2012; median follow-up time was 20 months.

End point values	GM-CSF	Talimogene Laherparepvec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	295		
Units: percentage of participants				
number (confidence interval 95%)	2.1 (0 to 4.5)	16.3 (12.1 to 20.5)		

Statistical analyses

Statistical analysis title	Treatment Difference

Statistical analysis description:

The null hypothesis was that there was no difference in the durable response rate between the talimogene laherparepvec and control arms. Study success was defined as the rejection of this hypothesis such that talimogene laherparepvec was found to be superior to GM-CSF using the 2-sided Fisher's exact test, with a p-value of ≤ 0.0488.

Comparison groups	Talimogene Laherparepvec v GM-CSF
Number of subjects included in analysis	436
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Fisher exact
Parameter estimate	Treatment Difference
Point estimate	14.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.3
upper limit	19

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival was defined as the time from the date of randomization to the date of death from any cause. Overall survival time was censored at the last date the patient was known to be alive when the confirmation of death was absent or unknown. Participants were censored at the date of randomization if no additional follow-up data were obtained.

End point type	Secondary

End point timeframe:

From randomization until the first 290 survival events had occurred (data cut-off date of 31 March 2014); median time on follow-up was 44 months.

End point values	GM-CSF	Talimogene Laherparepvec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	295		
Units: months				
median (confidence interval 95%)	18.9 (16 to 23.7)	23.3 (19.5 to 29.6)		

Statistical analyses

Statistical analysis title	Overall Survival Analysis

Statistical analysis description:

The primary method for analysis of overall survival was an unadjusted log-rank test. Testing of overall survival was conditional on a statistically significance difference in the primary endpoint of durable response. Success was defined as a p-value ≤ 0.05.

The hazard ratio was obtained from the unadjusted Cox Proportional Hazard Model. A hazard ratio < 1.0 indicates a lower average death rate and a longer overall survival for talimogene laherparepvec relative to GM-CSF.

Comparison groups	GM-CSF v Talimogene Laherparepvec
Number of subjects included in analysis	436
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0511
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	1

Secondary: Objective Response Rate

End point title	Objective Response Rate

End point description:

Objective response rate was defined as the percentage of participants with a best overall response of complete response (CR) or partial response (PR) assessed by the Endpoint Assessment Committee (EAC). Best overall response for a patient is the best overall response observed across all time points. Disease assessments were performed at the beginning of each treatment cycle and assessed in accordance with modified World Health Organization criteria.
CR: Disappearance of all clinical evidence of tumor (both measurable and non-measurable but evaluable disease); PR: ≥ 50% reduction in the sum of the products of the perpendicular diameters of all measurable tumors at the time of assessment as compared to baseline.

End point type	Secondary

End point timeframe:

From randomization until the data cut-off date of 21 December 2012; median follow-up time was 20 months.

End point values	GM-CSF	Talimogene Laherparepvec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	295		
Units: percentage of participants				
number (confidence interval 95%)	5.7 (1.9 to 9.5)	26.4 (21.4 to 31.5)		

Statistical analyses

Statistical analysis title	Objective Response Rate Treatment Difference
Comparison groups	GM-CSF v Talimogene Laherparepvec

Number of subjects included in analysis	436
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Fisher exact
Parameter estimate	Treatment Difference
Point estimate	20.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	14.4
upper limit	27.1

Notes:

[1] - Descriptive

Secondary: Duration of Response

End point title	Duration of Response

End point description:

The duration of response is defined as the longest individual period from entering response (CR or PR as assessed by the EAC) to the first documented evidence of the patient no longer meeting the criteria for being in response or death, whichever is earlier. Responses were censored at the last assessment showing response.
"99999" indicates data 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 21 December 2012; median follow-up time was 20 months.

End point values	GM-CSF	Talimogene Laherparepvec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8[2]	78[3]		
Units: months				
median (confidence interval 95%)	2.8 (1.2 to 99999)	99999 (99999 to 99999)		

Notes:

[2] - Participants with an objective response (CR or PR) per EAC assessment.

[3] - Participants with an objective response (CR or PR) per EAC assessment.

Statistical analyses

Statistical analysis title	Duration of Response Analysis

Statistical analysis description:

The hazard ratio was obtained from the unadjusted Cox Proportional Hazard Model. A hazard ratio < 1.0 indicates a longer average duration of response for talimogene laherparepvec relative to GM-CSF.

Comparison groups	GM-CSF v Talimogene Laherparepvec

Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0868 [4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.14
upper limit	1.18

Notes:

[4] - Descriptive

Secondary: Response Onset

End point title	Response Onset

End point description:

Response onset is defined as the time from the date of randomization to the date of the first documented evidence of response (CR or PR) per EAC assessment.

End point type	Secondary

End point timeframe:

From randomization until the data cut-off date of 21 December 2012; median follow-up time was 20 months.

End point values	GM-CSF	Talimogene Laherparepvec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8[5]	78[6]		
Units: months				
median (confidence interval 95%)	3.7 (1.9 to 5.6)	4.1 (3.8 to 5.4)		

Notes:

[5] - Participants with an objective response (CR or PR) per EAC assessment.

[6] - Participants with an objective response (CR or PR) per EAC assessment.

Statistical analyses

Statistical analysis title	Response Onset Analysis

Statistical analysis description:

The hazard ratio was obtained from the unadjusted Cox Proportional Hazard Model. A hazard ratio > 1.0 indicates a a higher average response onset rate for talimogene laherparepvec relative to GM-CSF.

Comparison groups	GM-CSF v Talimogene Laherparepvec
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.202 [7]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.62

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	1.3

Notes:

[7] - Descriptive

Secondary: Time to Treatment Failure

End point title	Time to Treatment Failure

End point description:

Time to treatment failure was assessed by the investigator, and calculated from randomization until the first clinically relevant disease progression where there is no response achieved after the progression, or until death if no such progression occurs. Participants who did not have clinically relevant progression or did not die were censored at the time of the their last tumor assessment. Participants who withdrew from treatment due to a clinically unacceptable toxicity were not considered as an event in the analysis. Progressive disease (PD) is defined as a ≥ 25% increase in the sum of the products of the perpendicular diameters of all measurable tumors since baseline, or the unequivocal appearance of a new tumor since the last response assessment time point.
Clinically relevant progressive disease is PD that is associated with a decline in performance status and/or in the opinion of the investigator the patient requires alternative therapy.

End point type	Secondary

End point timeframe:

From randomization until the data cut-off date of 21 December 2012; median follow-up time was 20 months.

End point values	GM-CSF	Talimogene Laherparepvec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	295		
Units: months				
median (confidence interval 95%)	2.9 (2.8 to 4)	8.2 (6.5 to 9.9)		

Statistical analyses

Statistical analysis title	Time to Treatment Failure Analysis

Statistical analysis description:

The hazard ratio was obtained from the unadjusted Cox Proportional Hazard Model. A hazard ratio < 1.0 indicates a longer average time to treatment failure for talimogene laherparepvec relative to GM-CSF.

Comparison groups	GM-CSF v Talimogene Laherparepvec
Number of subjects included in analysis	436
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [8]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.42

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.32
upper limit	0.54

Notes:

[8] - Descriptive

Secondary: Response Interval

End point title	Response Interval

End point description:

Response interval is defined as the interval between the date of randomization and the date of the last documented evidence of response (CR or PR as assessed by the Investigator) prior to any new anti-cancer therapy. Response Interval post response onset was censored if a patient was still in response at the last observation.
"99999" indicates data 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 21 December 2012; median follow-up time was 20 months.

End point values	GM-CSF	Talimogene Laherparepvec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9[9]	91[10]		
Units: months				
median (confidence interval 95%)	7.5 (1.9 to 99999)	99999 (99999 to 99999)		

Notes:

[9] - Participants with an objective response (CR or PR) per Investigator assessment.

[10] - Participants with an objective response (CR or PR) per Investigator assessment.

Statistical analyses

Statistical analysis title	Response Interval Analysis

Statistical analysis description:

The hazard ratio was obtained from the unadjusted Cox Proportional Hazard Model. A hazard ratio < 1.0 indicates a longer response interval for talimogene laherparepvec relative to GM-CSF.

Comparison groups	GM-CSF v Talimogene Laherparepvec
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005 [11]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.13
upper limit	0.73

Notes:
[11] - Descriptive

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose until 30 days after the last dose until the data cut off date of 8 August 2014; median treatment duration was 10.0 weeks (0.6 to 120.0 weeks) in the GM-CSF arm and 23.1 weeks (0.1 to 176.7 weeks) in the talimogene laherparepvec arm.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Talimogene Laherparepvec

Reporting group description:

Participants received talimogene laherparepvec on Days 1 and 15 of each 28-day cycle for 24 weeks. The initial dose was at a concentration of 10^6 PFU/mL, injected into 1 or more skin, subcutaneous or nodal tumors. Subsequent doses began at least 3 weeks after the first dose and consisted of talimogene laherparepvec at a concentration of 10^8 PFU/mL. Participants could continue treatment until clinically relevant disease progression, intolerability, withdrawal of consent, complete remission, lack of response by 12 months, or disappearance of all injectable lesions, for a maximum of 18 months.

Reporting group title	GM-CSF

Reporting group description:

GM-CSF was administered at a dose of 125 µg/m²/day subcutaneously for 14 days in 28-day cycles for 24 weeks. Participants could continue treatment until clinically relevant disease progression, intolerability, withdrawal of consent, complete remission, or lack of response by 12 months, for a maximum of 18 months.

Serious adverse events	Talimogene Laherparepvec	GM-CSF	
Total subjects affected by serious adverse events			
subjects affected / exposed	80 / 292 (27.40%)	17 / 127 (13.39%)	
number of deaths (all causes)	12	2	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder transitional cell carcinoma			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemangioma of liver			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			

subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected neoplasm			
subjects affected / exposed	3 / 292 (1.03%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melanoma recurrent			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	3 / 292 (1.03%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastatic malignant melanoma			
subjects affected / exposed	4 / 292 (1.37%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasmacytoma			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			

subjects affected / exposed	4 / 292 (1.37%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	3 / 292 (1.03%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasculitis			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic shock			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Disease progression			
subjects affected / exposed	10 / 292 (3.42%)	2 / 127 (1.57%)	
occurrences causally related to treatment / all	0 / 10	0 / 2	
deaths causally related to treatment / all	0 / 6	0 / 1	
Non-cardiac chest pain			
subjects affected / exposed	0 / 292 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	5 / 292 (1.71%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	5 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspiration			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial hyperreactivity			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 292 (0.68%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Obstructive airways disorder			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 292 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	4 / 292 (1.37%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuritic pain			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 292 (0.68%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	2 / 292 (0.68%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Psychiatric disorders			

Anxiety			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	2 / 292 (0.68%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Anaemia postoperative			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delayed recovery from anaesthesia			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle fracture			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 292 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pelvic fracture			
subjects affected / exposed	1 / 292 (0.34%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation associated pain			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seroma			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	2 / 292 (0.68%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound decomposition			
subjects affected / exposed	0 / 292 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 292 (0.34%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 292 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			

subjects affected / exposed	2 / 292 (0.68%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 292 (0.34%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Restrictive cardiomyopathy			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brain oedema			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	3 / 292 (1.03%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system lesion			

subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	2 / 292 (0.68%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocephalus			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	0 / 292 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	2 / 292 (0.68%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	2 / 292 (0.68%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	0 / 292 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 292 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	3 / 292 (1.03%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	2 / 292 (0.68%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intussusception			

subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal haemorrhage			
subjects affected / exposed	0 / 292 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 292 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 292 (0.68%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Pain of skin			
subjects affected / exposed	0 / 292 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Glomerulonephritis			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 292 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			

subjects affected / exposed	2 / 292 (0.68%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal papillary necrosis			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	0 / 292 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 292 (0.68%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			

subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column stenosis			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 292 (0.34%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	7 / 292 (2.40%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	5 / 7	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotitis			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic abscess			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Upper respiratory tract infection			

subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 292 (0.68%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperuricaemia			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			

subjects affected / exposed	0 / 292 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophagia			
subjects affected / exposed	1 / 292 (0.34%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Talimogene Laherparepvec	GM-CSF	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	282 / 292 (96.58%)	113 / 127 (88.98%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	20 / 292 (6.85%)	7 / 127 (5.51%)	
occurrences (all)	29	7	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	143 / 292 (48.97%)	11 / 127 (8.66%)	
occurrences (all)	377	28	
Fatigue			
subjects affected / exposed	148 / 292 (50.68%)	46 / 127 (36.22%)	
occurrences (all)	343	69	
Influenza like illness			
subjects affected / exposed	89 / 292 (30.48%)	19 / 127 (14.96%)	
occurrences (all)	335	37	
Injection site erythema			
subjects affected / exposed	15 / 292 (5.14%)	33 / 127 (25.98%)	
occurrences (all)	15	51	
Injection site reaction			
subjects affected / exposed	9 / 292 (3.08%)	12 / 127 (9.45%)	
occurrences (all)	13	19	
Injection site pruritus			

subjects affected / exposed	5 / 292 (1.71%)	21 / 127 (16.54%)	
occurrences (all)	7	26	
Injection site pain			
subjects affected / exposed	83 / 292 (28.42%)	8 / 127 (6.30%)	
occurrences (all)	146	11	
Injection site swelling			
subjects affected / exposed	11 / 292 (3.77%)	8 / 127 (6.30%)	
occurrences (all)	14	12	
Oedema peripheral			
subjects affected / exposed	38 / 292 (13.01%)	12 / 127 (9.45%)	
occurrences (all)	50	20	
Pain			
subjects affected / exposed	48 / 292 (16.44%)	13 / 127 (10.24%)	
occurrences (all)	67	19	
Pyrexia			
subjects affected / exposed	122 / 292 (41.78%)	11 / 127 (8.66%)	
occurrences (all)	301	24	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	18 / 292 (6.16%)	2 / 127 (1.57%)	
occurrences (all)	24	4	
Dyspnoea			
subjects affected / exposed	14 / 292 (4.79%)	14 / 127 (11.02%)	
occurrences (all)	16	19	
Cough			
subjects affected / exposed	31 / 292 (10.62%)	11 / 127 (8.66%)	
occurrences (all)	43	12	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	19 / 292 (6.51%)	2 / 127 (1.57%)	
occurrences (all)	21	2	
Depression			
subjects affected / exposed	16 / 292 (5.48%)	3 / 127 (2.36%)	
occurrences (all)	16	3	
Insomnia			

subjects affected / exposed	21 / 292 (7.19%)	6 / 127 (4.72%)	
occurrences (all)	22	7	
Investigations			
Weight decreased			
subjects affected / exposed	17 / 292 (5.82%)	1 / 127 (0.79%)	
occurrences (all)	22	1	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	15 / 292 (5.14%)	3 / 127 (2.36%)	
occurrences (all)	16	5	
Nervous system disorders			
Dizziness			
subjects affected / exposed	31 / 292 (10.62%)	4 / 127 (3.15%)	
occurrences (all)	34	4	
Headache			
subjects affected / exposed	55 / 292 (18.84%)	12 / 127 (9.45%)	
occurrences (all)	104	17	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	15 / 292 (5.14%)	2 / 127 (1.57%)	
occurrences (all)	22	2	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	27 / 292 (9.25%)	3 / 127 (2.36%)	
occurrences (all)	48	3	
Constipation			
subjects affected / exposed	34 / 292 (11.64%)	8 / 127 (6.30%)	
occurrences (all)	63	8	
Diarrhoea			
subjects affected / exposed	57 / 292 (19.52%)	14 / 127 (11.02%)	
occurrences (all)	82	24	
Dyspepsia			
subjects affected / exposed	15 / 292 (5.14%)	8 / 127 (6.30%)	
occurrences (all)	16	10	
Nausea			

subjects affected / exposed	106 / 292 (36.30%)	25 / 127 (19.69%)	
occurrences (all)	191	28	
Vomiting			
subjects affected / exposed	63 / 292 (21.58%)	12 / 127 (9.45%)	
occurrences (all)	96	15	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	22 / 292 (7.53%)	9 / 127 (7.09%)	
occurrences (all)	29	11	
Hyperhidrosis			
subjects affected / exposed	23 / 292 (7.88%)	9 / 127 (7.09%)	
occurrences (all)	34	15	
Night sweats			
subjects affected / exposed	6 / 292 (2.05%)	7 / 127 (5.51%)	
occurrences (all)	6	13	
Pruritus			
subjects affected / exposed	29 / 292 (9.93%)	19 / 127 (14.96%)	
occurrences (all)	37	33	
Rash			
subjects affected / exposed	27 / 292 (9.25%)	10 / 127 (7.87%)	
occurrences (all)	32	11	
Vitiligo			
subjects affected / exposed	18 / 292 (6.16%)	1 / 127 (0.79%)	
occurrences (all)	18	1	
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	15 / 292 (5.14%)	5 / 127 (3.94%)	
occurrences (all)	16	5	
Muscle spasms			
subjects affected / exposed	13 / 292 (4.45%)	7 / 127 (5.51%)	
occurrences (all)	14	10	
Back pain			
subjects affected / exposed	30 / 292 (10.27%)	8 / 127 (6.30%)	
occurrences (all)	46	9	
Arthralgia			

subjects affected / exposed	51 / 292 (17.47%)	11 / 127 (8.66%)	
occurrences (all)	71	14	
Musculoskeletal pain			
subjects affected / exposed	14 / 292 (4.79%)	7 / 127 (5.51%)	
occurrences (all)	20	7	
Myalgia			
subjects affected / exposed	52 / 292 (17.81%)	7 / 127 (5.51%)	
occurrences (all)	119	7	
Neck pain			
subjects affected / exposed	15 / 292 (5.14%)	7 / 127 (5.51%)	
occurrences (all)	18	8	
Pain in extremity			
subjects affected / exposed	48 / 292 (16.44%)	12 / 127 (9.45%)	
occurrences (all)	65	12	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	15 / 292 (5.14%)	2 / 127 (1.57%)	
occurrences (all)	22	2	
Upper respiratory tract infection			
subjects affected / exposed	30 / 292 (10.27%)	8 / 127 (6.30%)	
occurrences (all)	36	9	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	30 / 292 (10.27%)	14 / 127 (11.02%)	
occurrences (all)	34	15	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 November 2009	- Subjects with previously untreated melanoma were allowed to enroll. - Permitted medications were updated to allow for oral and systemic steroid use. - Baseline brain MRI was included as a measure to assess disease status. - The use of liquid GM-CSF was added.
08 July 2010	- Survival follow-up was increased from 2 years to 3 years from the time of randomization. - Subjects were allowed to continue to receive study treatment during corticosteroid therapy following stereotactic radiotherapy providing that the total daily dose did not exceed the equivalent of 10 mg prednisone. - Exclusion criteria were updated to allow subjects with a second cancer to enroll if they were diagnosed at a stage where definitive therapy results in near certain cure (with Medical Monitor approval). - Subjects with a total cumulative tumor burden in excess of 20 cm were allowed to enroll with Medical Monitor approval. - Injectable local anesthetic was allowed during talimogene laherparepvec administration, and procedures required during the 4-hour period after the first injection were clarified. - GM-CSF dosing modifications were clarified. - A photographic requirement for events of vitiligo was added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported