Clinical trial results:
A Phase 2, Open-Label, Single Arm Study to Evaluate the Safety and Efficacy of Pembrolizumab in Participants with Recurrent or Metastatic Cutaneous Squamous Cell Carcinoma (R/M cSCC)

Summary

EudraCT number	2017-000594-37
Trial protocol	DE ES GB
Global end of trial date	13 September 2023

Results information

Result version number	v1 (current)
This version publication date	05 September 2024
First version publication date	05 September 2024

Trial information

Trial identification

Sponsor protocol code	MK-3475-629

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme LLC
Sponsor organisation address	126 East Lincoln Avenue, P.O. Box 2000, Rahway, NJ, United States, 07065
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@merck.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	13 September 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 July 2020
Global end of trial reached?	Yes
Global end of trial date	13 September 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the safety and efficacy of pembrolizumab (MK-3475) in adult participants with recurrent or metastatic (R/M) cutaneous Squamous Cell Carcinoma (cSCC) or locally advanced (LA) unresectable cSCC that is not amenable to surgery and/or radiation and/or systemic therapies.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 October 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 25
Country: Number of subjects enrolled	Canada: 10
Country: Number of subjects enrolled	France: 44
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Israel: 16
Country: Number of subjects enrolled	Mexico: 11
Country: Number of subjects enrolled	Norway: 5
Country: Number of subjects enrolled	Spain: 17
Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	United States: 17
Worldwide total number of subjects	159
EEA total number of subjects	73

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	42
From 65 to 84 years	91
85 years and over	26

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

There were 2 cohorts in this study and each cohort received the same dose/treatment regimen. Baseline characteristics and outcome measures are presented by cohort. Adverse events were pre-specified to be reported as a single group by intervention for first and second course pembrolizumab.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Locally Advanced Unresectable cSCC Cohort

Arm description:

Participants received pembrolizumab 200 mg via IV infusion on Day 1 of each 3-week cycle for up to 35 doses (approximately 24 months).

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

Dosage and administration details:

200 mg administered as IV infusion on Day 1 of every 3-week cycle

Arm title	Recurrent or Metastatic Cutaneous cSCC Cohort

Arm description:

Participants received pembrolizumab 200 mg via intravenous (IV) infusion on Day 1 of each 3-week cycle for up to 35 doses (approximately 24 months).

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

Dosage and administration details:

200 mg administered as IV infusion on Day 1 of every 3-week cycle

Number of subjects in period 1	Locally Advanced Unresectable cSCC Cohort	Recurrent or Metastatic Cutaneous cSCC Cohort
Started	54	105
Received Second Course of Pembrolizumab	1	2
Completed	0	0
Not completed	54	105
Adverse event, serious fatal	24	70
Sponsor's decision	22	27
Consent withdrawn by subject	5	4
Physician decision	2	1
Lost to follow-up	1	3

Baseline characteristics

Reporting groups	
Reporting group title	Locally Advanced Unresectable cSCC Cohort
Reporting group description:	
Participants received pembrolizumab 200 mg via IV infusion on Day 1 of each 3-week cycle for up to 35 doses (approximately 24 months).	
Reporting group title	Recurrent or Metastatic Cutaneous cSCC Cohort
Reporting group description:	
Participants received pembrolizumab 200 mg via intravenous (IV) infusion on Day 1 of each 3-week cycle for up to 35 doses (approximately 24 months).	

Reporting group values	Locally Advanced Unresectable cSCC Cohort	Recurrent or Metastatic Cutaneous cSCC Cohort	Total
Number of subjects	54	105	159
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	11	31	42
From 65-84 years	32	59	91
85 years and over	11	15	26
Age Continuous Units: Years			
arithmetic mean	73.7	70.0	
standard deviation	± 12.4	± 14.3	-
Sex: Female, Male Units: Participants			
Female	15	25	40
Male	39	80	119
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	3	4
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	1	1
Black or African American	1	0	1
White	40	68	108
More than one race	0	1	1
Unknown or Not Reported	12	32	44
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	2	13	15
Not Hispanic or Latino	40	57	97

Unknown or Not Reported	12	35	47

End points

End points reporting groups

Reporting group title	Locally Advanced Unresectable cSCC Cohort
Reporting group description:	
Participants received pembrolizumab 200 mg via IV infusion on Day 1 of each 3-week cycle for up to 35 doses (approximately 24 months).	
Reporting group title	Recurrent or Metastatic Cutaneous cSCC Cohort
Reporting group description:	
Participants received pembrolizumab 200 mg via intravenous (IV) infusion on Day 1 of each 3-week cycle for up to 35 doses (approximately 24 months).	

Primary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)[1]
End point description:	
ORR was defined as the percentage of participants who have best response of Complete Response (CR: Disappearance of all target lesions) or Partial Response (PR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). ORR per RECIST 1.1 as assessed by blinded independent central review (BICR) is presented. The analysis population consisted of all participants who received ≥1 dose of study treatment.	
End point type	Primary
End point timeframe:	
Up to approximately 32 months	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No between-group statistical analyses were performed for this endpoint.

End point values	Locally Advanced Unresectable cSCC Cohort	Recurrent or Metastatic Cutaneous cSCC Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	105		
Units: Percentage of participants				
number (confidence interval 95%)	51.9 (37.8 to 65.7)	35.2 (26.2 to 45.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR)

End point title	Disease Control Rate (DCR)
End point description:	
DCR is defined as the percentage of participants who have a CR or PR or Stable Disease (SD: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease). The DCR per RECIST 1.1 as assessed by BICR is presented. The analysis population consisted of all participants who received ≥1 dose of study treatment.	

End point type	Secondary

End point timeframe:

Up to approximately 56 months

End point values	Locally Advanced Unresectable cSCC Cohort	Recurrent or Metastatic Cutaneous cSCC Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	105		
Units: Percentage of participants				
number (confidence interval 95%)	64.8 (50.6 to 77.3)	52.4 (42.4 to 62.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

For participants who demonstrated a confirmed CR or PR per RECIST 1.1, DOR was defined as the time from first documented evidence of a CR or PR until progressive disease (PD) or death. Per RECIST 1.1, PD was defined as at least a 20% increase in the sum of diameters of target lesions as well as an absolute increase of at least a 5 mm in the sum of diameters. The appearance of one or more new lesions was also considered PD. The DOR per RECIST 1.1 as assessed by BICR is presented for all participants who experienced a confirmed CR or PR. The analysis population consisted of all participants who received ≥1 dose of study treatment and had confirmed complete response or partial response.

End point type	Secondary

End point timeframe:

Up to approximately 56 months

End point values	Locally Advanced Unresectable cSCC Cohort	Recurrent or Metastatic Cutaneous cSCC Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	37		
Units: Months				
median (full range (min-max))	2.7 (1.1 to 12.3)	1.6 (1.2 to 24.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)

End point description:

PFS was defined as the time from first dose of study treatment to the first documented PD or death due to any cause, whichever occurred first. PFS per RECIST 1.1 as assessed by BICR is presented. The analysis population consisted of all participants who received ≥1 dose of study treatment.

End point type	Secondary

End point timeframe:

Up to approximately 56 months

End point values	Locally Advanced Unresectable cSCC Cohort	Recurrent or Metastatic Cutaneous cSCC Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	105		
Units: Months				
median (confidence interval 95%)	14.4 (5.5 to 43.6)	5.7 (3.1 to 8.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from first dose of study treatment to death due to any cause. The OS for all participants is presented. The analysis population consisted of all participants who received ≥1 dose of study treatment. A value of 9999 indicates that median and upper limit were not reached at time of data cut-off due to insufficient number of participants with an event.

End point type	Secondary

End point timeframe:

Up to approximately 56 months

End point values	Locally Advanced Unresectable cSCC Cohort	Recurrent or Metastatic Cutaneous cSCC Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	105		
Units: Months				
median (confidence interval 95%)	9999 (33.3 to 9999)	23.8 (13.4 to 30.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Experienced One or More Adverse Events (AEs)

End point title	Number of Participants Who Experienced One or More Adverse Events (AEs)

End point description:

An AE is defined as any unfavorable and unintended sign, symptom, or disease (new or worsening) temporally associated with the use of study therapy, regardless of whether or not a causal relationship with the study therapy. The number of participants who experienced an AE is presented. The analysis population consisted of all participants who received ≥1 dose of study treatment.

End point type	Secondary

End point timeframe:

Up to approximately 56 months

End point values	Locally Advanced Unresectable cSCC Cohort	Recurrent or Metastatic Cutaneous cSCC Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	105		
Units: Participants	51	102		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Discontinued Study Treatment Due to AE

End point title	Number of Participants Who Discontinued Study Treatment Due to AE

End point description:

An AE is defined as any unfavorable and unintended sign, symptom, or disease (new or worsening) temporally associated with the use of study therapy, regardless of whether or not a causal relationship with the study therapy. The number of participants who discontinued study treatment due to an AE is presented. The analysis population consisted of all participants who received ≥1 dose of study treatment.

End point type	Secondary

End point timeframe:

Up to approximately 56 months

End point values	Locally Advanced Unresectable cSCC Cohort	Recurrent or Metastatic Cutaneous cSCC Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	105		
Units: Participants	11	20		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 56 months

Adverse event reporting additional description:

All participants who received ≥1 dose of study treatment are included. AEs were pre-specified to be reported as a single group by intervention for first course and second course. Per protocol, disease progression was not considered an AE unless considered related to study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	R/M Cutaneous and LA Unresectable cSCC Second Course

Reporting group description:

Eligible participants who stopped the initial course of pembrolizumab but progressed after discontinuation may have been able to initiate a second course of pembrolizumab for up to 17 cycles (up to approximately 1 additional year) at the investigator's discretion.

Reporting group title	R/M Cutaneous and LA Unresectable cSCC First Course

Reporting group description:

Participants received pembrolizumab 200 mg via intravenous (IV) infusion on Day 1 of each 3-week cycle for up to 35 doses (approximately 24 months).

Serious adverse events	R/M Cutaneous and LA Unresectable cSCC Second Course	R/M Cutaneous and LA Unresectable cSCC First Course	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 3 (66.67%)	87 / 159 (54.72%)	
number of deaths (all causes)	1	97	
number of deaths resulting from adverse events	0	20	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuroendocrine carcinoma of the skin			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neoplasm recurrence			

subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelodysplastic syndrome			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lentigo maligna			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected neoplasm			
subjects affected / exposed	0 / 3 (0.00%)	3 / 159 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Basal cell carcinoma			
subjects affected / exposed	0 / 3 (0.00%)	9 / 159 (5.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 19	
deaths causally related to treatment / all	0 / 0	0 / 0	
B-cell lymphoma			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	1 / 3 (33.33%)	2 / 159 (1.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Tumour pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Giant cell arteritis			

subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Superior vena cava occlusion			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 3 (0.00%)	2 / 159 (1.26%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 3 (0.00%)	2 / 159 (1.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dyspnoea			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Investigations			
Transaminases increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Wound complication			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Radiation necrosis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoradionecrosis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint injury			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 3 (0.00%)	2 / 159 (1.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			

subjects affected / exposed	0 / 3 (0.00%)	2 / 159 (1.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial infarction			
subjects affected / exposed	0 / 3 (0.00%)	2 / 159 (1.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			
subjects affected / exposed	0 / 3 (0.00%)	2 / 159 (1.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ventricular extrasystoles			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Epilepsy			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cranial nerve disorder			

subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cerebrospinal fluid leakage			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 3 (0.00%)	3 / 159 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolytic anaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Abdominal pain lower			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wall haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 3 (0.00%)	2 / 159 (1.26%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Constipation			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer perforation			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 3 (0.00%)	2 / 159 (1.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hypertransaminasaemia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 159 (1.26%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 3 (33.33%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune hepatitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Photosensitivity reaction			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune nephritis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prerenal failure			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Lymphocytic hypophysitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adrenal insufficiency			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
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			
Osteoarthritis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Arthralgia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			

subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess neck			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia			
subjects affected / exposed	0 / 3 (0.00%)	5 / 159 (3.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Otitis externa			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral candidiasis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			

subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Infestation			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis salmonella			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal skin infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermo-hypodermitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			

subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Scrotal cellulitis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 159 (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 / 3 (33.33%)	4 / 159 (2.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Septic shock			
subjects affected / exposed	0 / 3 (0.00%)	2 / 159 (1.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Soft tissue infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 3 (0.00%)	2 / 159 (1.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			

subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophagia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	R/M Cutaneous and LA Unresectable cSCC Second Course	R/M Cutaneous and LA Unresectable cSCC First Course	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 3 (66.67%)	139 / 159 (87.42%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 3 (33.33%)	6 / 159 (3.77%)	
occurrences (all)	1	6	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 3 (33.33%)	35 / 159 (22.01%)	
occurrences (all)	1	44	
Chest pain			
subjects affected / exposed	0 / 3 (0.00%)	8 / 159 (5.03%)	
occurrences (all)	0	8	
Fatigue			

subjects affected / exposed	0 / 3 (0.00%)	35 / 159 (22.01%)	
occurrences (all)	0	39	
Oedema peripheral			
subjects affected / exposed	0 / 3 (0.00%)	17 / 159 (10.69%)	
occurrences (all)	0	21	
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	14 / 159 (8.81%)	
occurrences (all)	0	17	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 3 (0.00%)	13 / 159 (8.18%)	
occurrences (all)	0	13	
Cough			
subjects affected / exposed	0 / 3 (0.00%)	19 / 159 (11.95%)	
occurrences (all)	0	23	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 3 (0.00%)	10 / 159 (6.29%)	
occurrences (all)	0	10	
Investigations			
Weight decreased			
subjects affected / exposed	0 / 3 (0.00%)	18 / 159 (11.32%)	
occurrences (all)	0	19	
Protein total decreased			
subjects affected / exposed	1 / 3 (33.33%)	1 / 159 (0.63%)	
occurrences (all)	3	7	
Blood urea increased			
subjects affected / exposed	1 / 3 (33.33%)	2 / 159 (1.26%)	
occurrences (all)	2	2	
Blood phosphorus decreased			
subjects affected / exposed	1 / 3 (33.33%)	2 / 159 (1.26%)	
occurrences (all)	1	2	
Blood creatinine increased			
subjects affected / exposed	0 / 3 (0.00%)	8 / 159 (5.03%)	
occurrences (all)	0	8	
Blood bilirubin increased			

subjects affected / exposed	1 / 3 (33.33%)	3 / 159 (1.89%)	
occurrences (all)	1	4	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 3 (0.00%)	11 / 159 (6.92%)	
occurrences (all)	0	13	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 3 (0.00%)	11 / 159 (6.92%)	
occurrences (all)	0	12	
Headache			
subjects affected / exposed	0 / 3 (0.00%)	18 / 159 (11.32%)	
occurrences (all)	0	20	
Paraesthesia			
subjects affected / exposed	1 / 3 (33.33%)	6 / 159 (3.77%)	
occurrences (all)	1	6	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 3 (0.00%)	18 / 159 (11.32%)	
occurrences (all)	0	26	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	16 / 159 (10.06%)	
occurrences (all)	0	22	
Nausea			
subjects affected / exposed	0 / 3 (0.00%)	23 / 159 (14.47%)	
occurrences (all)	0	29	
Diarrhoea			
subjects affected / exposed	1 / 3 (33.33%)	31 / 159 (19.50%)	
occurrences (all)	1	38	
Constipation			
subjects affected / exposed	0 / 3 (0.00%)	40 / 159 (25.16%)	
occurrences (all)	0	47	
Abdominal pain			
subjects affected / exposed	0 / 3 (0.00%)	13 / 159 (8.18%)	
occurrences (all)	0	14	

Skin and subcutaneous tissue disorders			
Skin lesion			
subjects affected / exposed	0 / 3 (0.00%)	10 / 159 (6.29%)	
occurrences (all)	0	19	
Rash			
subjects affected / exposed	0 / 3 (0.00%)	25 / 159 (15.72%)	
occurrences (all)	0	34	
Dry skin			
subjects affected / exposed	0 / 3 (0.00%)	11 / 159 (6.92%)	
occurrences (all)	0	11	
Actinic keratosis			
subjects affected / exposed	0 / 3 (0.00%)	9 / 159 (5.66%)	
occurrences (all)	0	15	
Pruritus			
subjects affected / exposed	0 / 3 (0.00%)	39 / 159 (24.53%)	
occurrences (all)	0	45	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 3 (0.00%)	14 / 159 (8.81%)	
occurrences (all)	0	16	
Musculoskeletal and connective tissue disorders			
Neck pain			
subjects affected / exposed	0 / 3 (0.00%)	8 / 159 (5.03%)	
occurrences (all)	0	8	
Muscle spasms			
subjects affected / exposed	1 / 3 (33.33%)	2 / 159 (1.26%)	
occurrences (all)	1	2	
Back pain			
subjects affected / exposed	0 / 3 (0.00%)	14 / 159 (8.81%)	
occurrences (all)	0	15	
Arthralgia			
subjects affected / exposed	0 / 3 (0.00%)	22 / 159 (13.84%)	
occurrences (all)	0	26	
Pain in extremity			
subjects affected / exposed	0 / 3 (0.00%)	26 / 159 (16.35%)	
occurrences (all)	0	29	

Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 3 (0.00%)	8 / 159 (5.03%)	
occurrences (all)	0	8	
Urinary tract infection			
subjects affected / exposed	0 / 3 (0.00%)	8 / 159 (5.03%)	
occurrences (all)	0	10	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 3 (0.00%)	25 / 159 (15.72%)	
occurrences (all)	0	27	
Hyponatraemia			
subjects affected / exposed	1 / 3 (33.33%)	4 / 159 (2.52%)	
occurrences (all)	1	7	
Hypocalcaemia			
subjects affected / exposed	1 / 3 (33.33%)	4 / 159 (2.52%)	
occurrences (all)	2	4	
Hyperchloraemia			
subjects affected / exposed	1 / 3 (33.33%)	1 / 159 (0.63%)	
occurrences (all)	2	1	
Hypercalcaemia			
subjects affected / exposed	0 / 3 (0.00%)	8 / 159 (5.03%)	
occurrences (all)	0	10	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 April 2018	Amendment 01: Primary reason for amendment was to add inclusion of first-line participants.
28 September 2018	Amendment 03: Primary reason for amendment was to add a cohort.
06 July 2021	Amendment 04: Primary reason for amendment was to incorporate revisions the dose modification and toxicity management guidelines.
29 March 2023	Amendment 06: Primary reason for amendment was to add language to allow participants to continue in a pembrolizumab extension study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported