Clinical trial results:
A Phase 2 Study in First Line Metastatic or Unresectable, Recurrent Head and Neck Squamous Cell Carcinoma to Evaluate Intratumoral MK-1454 in Combination with IV Pembrolizumab vs IV Pembrolizumab Monotherapy

Summary

EudraCT number	2019-003060-42
Trial protocol	NO ES FR GB
Global end of trial date	30 September 2022

Results information

Result version number	v1
This version publication date	13 October 2023
First version publication date	13 October 2023

Trial information

Trial identification

Sponsor protocol code	1454-002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04220866
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme LLC
Sponsor organisation address	126 East Lincoln Avenue,, Rahway, NJ, United States, P.O. Box 2000
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	30 September 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 September 2022
Global end of trial reached?	Yes
Global end of trial date	30 September 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to assess the efficacy and safety of intratumoral (IT) ulevostinag PLUS pembrolizumab (MK-3475) compared to pembrolizumab alone as a first line treatment of adults with metastatic or unresectable, recurrent head and neck squamous cell carcinoma (HNSCC).
The primary study hypotheses are that IT ulevostinag in combination with pembrolizumab results in a superior Objective Response Rate (ORR), per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1), compared to pembrolizumab alone:
1. In participants with a tumor that has a programmed cell death-ligand 1 (PD-L1) Combined Positive Scoring (CPS) ≥ 1, and
2. In participants with a tumor that has a PD-L1 CPS ≥ 20.

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	04 March 2022
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Israel: 4
Country: Number of subjects enrolled	Korea, Republic of: 1
Country: Number of subjects enrolled	Norway: 1
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	United States: 4
Worldwide total number of subjects	18
EEA total number of subjects	8

Notes:

Subjects enrolled per age group

In utero	0

Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	10
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Adults with a confirmed diagnosis of metastatic or unresectable, recurrent head and neck squamous cell carcinoma (HNSCC) with a tumor programmed cell death-1 ligand 1 (PD-L1) immunohistochemistry (IHC) combined positive scoring (CPS) ≥1 and had at least 1 measurable lesion that was amenable to intratumor (IT) injection were enrolled in this study.

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	Ulevostinag + Pembrolizumab

Arm description:

Participants received ulevostinag 540 ug via intratumoral (IT) injection on Day 1 of every week for two 3-week cycles (Cycles 1-2), then on Day 1 of each 3-week cycle for up 33 cycles (Cycles 3-35), for a total of 35 cycles PLUS pembrolizumab 200 mg via intravenous (IV) infusion on Day 1 of each 3-week cycle for up to 35 cycles. The total duration of treatment was up to approximately 2 years.

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

Dosage and administration details:

Participants received pembrolizumab 200 mg via IV infusion on Day 1 of each 3-week cycle for up to 35 cycles. The total duration of treatment is up to approximately 2 years

Investigational medicinal product name	Ulevostinag
Investigational medicinal product code	
Other name	MK-1454
Pharmaceutical forms	Injection
Routes of administration	Intratumoral use

Dosage and administration details:

Participants received ulevostinag 540 ug via intratumoral (IT) injection on Day 1 of every week for two 3-week cycles (Cycles 1-2), then on Day 1 of each 3-week cycle for up 33 cycles (Cycles 3-35), for a total of 35 cycles

Arm title	Pembrolizumab

Arm description:

Participants received pembrolizumab 200 mg via IV infusion on Day 1 of each 3-week cycle for up to 35 cycles. The total duration of treatment is up to approximately 2 years.

Arm type	Active comparator

Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	MK-3475 KEYTRUDA®
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received pembrolizumab 200 mg via IV infusion on Day 1 of each 3-week cycle for up to 35 cycles. The total duration of treatment is up to approximately 2 years

Number of subjects in period 1	Ulevostinag + Pembrolizumab	Pembrolizumab
Started	8	10
Completed	0	0
Not completed	8	10
Adverse event, serious fatal	4	5
Participation in the study terminated By Sponsor	2	4
Consent withdrawn by subject	-	1
Participation at the site terminated By Sponsor	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Ulevostinag + Pembrolizumab
Reporting group description:	
Participants received ulevostinag 540 ug via intratumoral (IT) injection on Day 1 of every week for two 3-week cycles (Cycles 1-2), then on Day 1 of each 3-week cycle for up 33 cycles (Cycles 3-35), for a total of 35 cycles PLUS pembrolizumab 200 mg via intravenous (IV) infusion on Day 1 of each 3-week cycle for up to 35 cycles. The total duration of treatment was up to approximately 2 years.	
Reporting group title	Pembrolizumab
Reporting group description:	
Participants received pembrolizumab 200 mg via IV infusion on Day 1 of each 3-week cycle for up to 35 cycles. The total duration of treatment is up to approximately 2 years.	

Reporting group values	Ulevostinag + Pembrolizumab	Pembrolizumab	Total
Number of subjects	8	10	18
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)	3	7	10
From 65-84 years	5	3	8
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	65.3	59.8	
standard deviation	± 9.8	± 9.8	-
Sex: Female, Male Units:			
Female	0	1	1
Male	8	9	17
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	1	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	8	9	17
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	8	10	18

Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	Ulevostinag + Pembrolizumab
Reporting group description:	
Participants received ulevostinag 540 ug via intratumoral (IT) injection on Day 1 of every week for two 3-week cycles (Cycles 1-2), then on Day 1 of each 3-week cycle for up 33 cycles (Cycles 3-35), for a total of 35 cycles PLUS pembrolizumab 200 mg via intravenous (IV) infusion on Day 1 of each 3-week cycle for up to 35 cycles. The total duration of treatment was up to approximately 2 years.	
Reporting group title	Pembrolizumab
Reporting group description:	
Participants received pembrolizumab 200 mg via IV infusion on Day 1 of each 3-week cycle for up to 35 cycles. The total duration of treatment is up to approximately 2 years.	

Primary: Objective Response Rate (ORR) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)

End point title	Objective Response Rate (ORR) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)[1]
End point description:	
ORR was defined as the percentage of participants in the analysis population who have a Complete Response (CR: Disappearance of all target lesions) or a Partial Response (PR: At least a 30% decrease in the sum of diameters of target lesions) per RECIST 1.1. ORR was assessed by blinded independent central review (BICR), and the 95% confidence interval (CI) was based on the exact method for binomial data. The population analyzed was all randomized participants based on the treatment arm to which they were randomized.	
End point type	Primary
End point timeframe:	
Up to 1088.0 days	
Notes:	
[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: Statistical comparisons between treatment groups were neither planned nor performed for this primary endpoint.	

End point values	Ulevostinag + Pembrolizumab	Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	10		
Units: Percentage of participants				
number (confidence interval 95%)	50.0 (15.7 to 84.3)	10.0 (0.3 to 44.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants discontinuing study treatment due to an AE

End point title	Number of participants discontinuing study treatment due to an AE
End point description:	
An AE is any untoward medical occurrence in a participant, temporally associated with the use of study	

treatment, whether or not considered related to the study treatment. The population analyzed was all randomized participants who received at least 1 dose of study treatment.

End point type	Secondary

End point timeframe:

Up to approximately 715.0 days

End point values	Ulevostinag + Pembrolizumab	Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	10		
Units: Participants	3	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS is defined as the time from randomization to the date of death from any cause, and is based on the product-limit (Kaplan-Meier) method for censored data. The population analyzed was all randomized participants based on the treatment arm to which they were randomized.

End point type	Secondary

End point timeframe:

Up to 1088.0 days

End point values	Ulevostinag + Pembrolizumab	Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8[2]	10[3]		
Units: Months				
median (confidence interval 95%)	99999 (1.0 to 99999)	11.1 (0.8 to 99999)		

Notes:

[2] - 99999 = Median and upper limit not reached due to insufficient number of participants with an event.
[3] - 99999 = Median and upper limit not reached due to insufficient number of participants with an event.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants who experienced an Adverse Event (AE)

End point title	Number of participants who experienced an Adverse Event (AE)

End point description:

An AE is any untoward medical occurrence in a participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. The population analyzed was all randomized participants who received at least 1 dose of study treatment.

End point type	Secondary

End point timeframe:

Up to 1088.0 days

End point values	Ulevostinag + Pembrolizumab	Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	10		
Units: Participants	8	10		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)

End point title	Progression-free Survival (PFS) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)

End point description:

PFS was defined as the time from randomization to the first documented progressive disease (PD) or death from any cause, whichever occurs first. Per RECIST 1.1, PD was defined as at least a 20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions was also considered PD. PFS was assessed by BICR and was based on the product-limit (Kaplan-Meier) method for censored data. The population analyzed was all randomized participants based on the treatment arm to which they were randomized.

End point type	Secondary

End point timeframe:

Up to 1088.0 days

End point values	Ulevostinag + Pembrolizumab	Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8[4]	10[5]		
Units: Months				
median (confidence interval 95%)	6.4 (1.0 to 99999)	1.5 (0.5 to 99999)		

Notes:

[4] - 99999 = Upper limit not reached due to insufficient number of participants with an even

[5] - 99999 = Upper limit not reached due to insufficient number of participants with an even

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)

End point title	Duration of Response (DOR) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)

End point description:

DOR was defined as the time from the first documented evidence of a Complete Response (CR: Disappearance of all target lesions) or a Partial Response (PR: At least a 30% decrease in the sum of diameters of target lesions) per RECIST 1.1 until Progressive Disease (PD) or death due to any cause, whichever occurs first, in participants demonstrating a CR or PR. Per RECIST 1.1, PD is defined as at least a 20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered PD. DOR was based on the product-limit (Kaplan-Meier) method for censored data. The population analyzed was all randomized participants based on the treatment arm to which they were randomized.

End point type	Secondary

End point timeframe:

Up to 1088.0 days

End point values	Ulevostinag + Pembrolizumab	Pembrolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8[6]	10[7]		
Units: Months				
median (full range (min-max))	99999 (99999 to 99999)	99999 (99999 to 99999)		

Notes:

[6] - .99999 = Results not reached due to insufficient number of responding participants with relapse

[7] - .99999 = Results not reached due to insufficient number of responding participants with relapse

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs): from first treatment up to 1088.0 days. All Cause Mortality (ACM): from randomization up to 1088.0 days.:

Adverse event reporting additional description:

The ACM population consisted of all randomized participants. The AE population consisted of all randomized participants who received at least1 dose of study treatment. Per protocol the following AE preferred terms not related to the drug were excluded: Neoplasm progression, Malignant neoplasm progression and Disease progression.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Pembrolizumab

Reporting group description:

Participants received pembrolizumab 200 mg via IV infusion on Day 1 of each 3-week cycle for up to 35 cycles. The total duration of treatment is up to approximately 2 years

Reporting group title	Ulevostinag + Pembrolizumab

Reporting group description:

Participants received ulevostinag 540 ug via intratumoral (IT) injection on Day 1 of every week for two 3-week cycles (Cycles 1-2), then on Day 1 of each 3-week cycle for up 33 cycles (Cycles 3-35), for a total of 35 cycles PLUS pembrolizumab 200 mg via intravenous (IV) infusion on Day 1 of each 3-week cycle for up to 35 cycles. The total duration of treatment was up to approximately 2 years.

Serious adverse events	Pembrolizumab	Ulevostinag + Pembrolizumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 10 (40.00%)	5 / 8 (62.50%)	
number of deaths (all causes)	5	4	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour haemorrhage			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (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			
Injection related reaction			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Wound haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Pericarditis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carotid artery aneurysm			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
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			
Injection site ulcer			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
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			
Acute respiratory failure			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuritic pain			

subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (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	1 / 10 (10.00%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis aspiration			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Infections and infestations			
COVID-19 pneumonia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sepsis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
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	Pembrolizumab	Ulevostinag + Pembrolizumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 10 (90.00%)	8 / 8 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm swelling			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	

Skin neoplasm bleeding			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Tumour inflammation			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Axillary pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Asthenia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 8 (12.50%)	
occurrences (all)	1	1	
Chills			
subjects affected / exposed	0 / 10 (0.00%)	2 / 8 (25.00%)	
occurrences (all)	0	5	
Swelling face			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	2	
Swelling			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	0 / 10 (0.00%)	4 / 8 (50.00%)	
occurrences (all)	0	10	
Injection site swelling			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	2	
Injection site reaction			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Injection site pain			

subjects affected / exposed	0 / 10 (0.00%)	4 / 8 (50.00%)	
occurrences (all)	0	6	
Injection site necrosis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Injection site erythema			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	2	
Influenza like illness			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	2 / 10 (20.00%)	1 / 8 (12.50%)	
occurrences (all)	2	1	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Dyspnoea			
subjects affected / exposed	1 / 10 (10.00%)	1 / 8 (12.50%)	
occurrences (all)	1	1	
Epistaxis			
subjects affected / exposed	0 / 10 (0.00%)	2 / 8 (25.00%)	
occurrences (all)	0	2	
Nasal cavity mass			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Productive cough			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Rhinorrhoea			

subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Depression			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 8 (12.50%)	
occurrences (all)	1	1	
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Blood creatinine increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Liver function test abnormal			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Tri-iodothyronine free increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	

Stoma site discharge			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Vascular pseudoaneurysm			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Congenital, familial and genetic disorders			
Tracheo-oesophageal fistula			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Nervous system disorders			
Anosmia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Dizziness			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Dysgeusia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Speech disorder			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 8 (12.50%)	
occurrences (all)	1	1	
Leukopenia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Lymphopenia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 8 (12.50%)	
occurrences (all)	1	1	
Lymphadenitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	

Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Hyperacusis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Vision blurred			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 10 (0.00%)	2 / 8 (25.00%)	
occurrences (all)	0	4	
Palatal disorder			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Oral pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	0 / 10 (0.00%)	3 / 8 (37.50%)	
occurrences (all)	0	3	
Impaired gastric emptying			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Dysphagia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Dry mouth			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Diarrhoea			

subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	2	
Constipation			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Colitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	3 / 10 (30.00%)	0 / 8 (0.00%)	
occurrences (all)	3	0	
Dry skin			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Drug eruption			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Dermatitis acneiform			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Skin burning sensation			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Sensitive skin			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Rash			
subjects affected / exposed	1 / 10 (10.00%)	1 / 8 (12.50%)	
occurrences (all)	1	1	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 10 (10.00%)	1 / 8 (12.50%)	
occurrences (all)	1	1	
Haematuria			

subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Proteinuria			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Renal impairment			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Bone pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Neck pain			
subjects affected / exposed	1 / 10 (10.00%)	1 / 8 (12.50%)	
occurrences (all)	1	1	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Tongue fungal infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Soft tissue infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Sinusitis			

subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Relapsing fever			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Pyuria			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Pneumonia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	2	
Hepatitis C			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Cellulitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Candida infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
COVID-19			
subjects affected / exposed	1 / 10 (10.00%)	1 / 8 (12.50%)	
occurrences (all)	1	1	
Bacteriuria			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Bacterial disease carrier			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 10 (10.00%)	3 / 8 (37.50%)	
occurrences (all)	1	3	
Dehydration			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	

Hypercalcaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	
occurrences (all)	2	0	
Hyperkalaemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Hyperphosphataemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Hypoalbuminaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Hypokalaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Hypomagnesaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Hyponatraemia			
subjects affected / exposed	2 / 10 (20.00%)	0 / 8 (0.00%)	
occurrences (all)	2	0	
Hypophosphataemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 September 2020	Amendment 1:To address Health Authority requests, including to provide rationale for minimum creatinine clearance in the eligibility criteria, to add clarification for PD-L1 testing to the protocol, to clarify ongoing safety monitoring during the conduct of the clinical trial, and to provide additional clarifications.
16 August 2021	Amendment 2: To update the dose modification and toxicity management guidelines for irAEs associated with pembrolizumab.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported