



Clinical trial results:

A Phase II Study of Pembrolizumab Monotherapy in Third-line Previously Treated Subjects with Advanced/Metastatic Adenocarcinoma or Squamous Cell Carcinoma of the Esophagus or Advanced/Metastatic Siewert Type I Adenocarcinoma of the Esophagogastric Junction (KEYNOTE -180)

Summary

EudraCT number	2015-002427-26
Trial protocol	DE GB DK FR
Global end of trial date	29 October 2021

Results information

Result version number	v1 (current)
This version publication date	23 September 2022
First version publication date	23 September 2022

Trial information

Trial identification

Sponsor protocol code	3475-180
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02559687
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	29 October 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 July 2018
Global end of trial reached?	Yes
Global end of trial date	29 October 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

In this study participants with advanced/metastatic adenocarcinoma of the esophagus (EAC), squamous cell carcinoma of the esophagus (ESCC), or advanced/metastatic Siewert type I adenocarcinoma of the esophagogastric junction (EGJ), who had been previously treated with two standard therapies, were treated with pembrolizumab.

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	02 December 2015
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: 4
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	France: 15
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	Japan: 30
Country: Number of subjects enrolled	Korea, Republic of: 9
Country: Number of subjects enrolled	Norway: 1
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	United States: 43
Worldwide total number of subjects	121
EEA total number of subjects	24

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)	57
From 65 to 84 years	63
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Of 185 participants screened for inclusion, 121 were enrolled and received treatment. Per protocol, response/progression or adverse events (AEs) that occurred during the second course were not counted towards efficacy outcome measures or safety outcome measures, respectively.

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

Arm title	Pembrolizumab 200 mg
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Arm description:

Participants received pembrolizumab 200 mg, intravenously (IV), every 3 weeks (Q3W) for up to 35 treatments (approximately 2 years). Eligible participants who stopped the initial course of pembrolizumab with Stable Disease (SD) or better but progressed after discontinuation may have been able to initiate a second course of pembrolizumab for up to an additional 17 trial treatments (up to approximately 1 additional year) at the investigator's discretion.

Arm type	Experimental
Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:

pembrolizumab 200 mg, intravenously (IV), every 3 weeks (Q3W) for up to 35 treatments

Number of subjects in period 1	Pembrolizumab 200 mg
Started	121
Received First Course of Pembrolizumab	121
Received Second Course of Pembrolizumab	1
Completed	0
Not completed	121
Adverse event, serious fatal	112
Consent withdrawn by subject	4
Sponsor Decision	5

Baseline characteristics

Reporting groups

Reporting group title	Pembrolizumab 200 mg
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Reporting group description:

Participants received pembrolizumab 200 mg, intravenously (IV), every 3 weeks (Q3W) for up to 35 treatments (approximately 2 years). Eligible participants who stopped the initial course of pembrolizumab with Stable Disease (SD) or better but progressed after discontinuation may have been able to initiate a second course of pembrolizumab for up to an additional 17 trial treatments (up to approximately 1 additional year) at the investigator's discretion.

Reporting group values	Pembrolizumab 200 mg	Total	
Number of subjects	121	121	
Age categorical			
Units: Subjects			

Age Continuous			
Units: Years			
arithmetic mean	63.5		
standard deviation	± 10.6	-	
Sex: Female, Male			
Units: Participants			
Female	21	21	
Male	100	100	
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	42	42	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	2	2	
White	71	71	
More than one race	0	0	
Unknown or Not Reported	6	6	
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	2	2	
Not Hispanic or Latino	108	108	
Unknown or Not Reported	11	11	

End points

End points reporting groups

Reporting group title	Pembrolizumab 200 mg
Reporting group description: Participants received pembrolizumab 200 mg, intravenously (IV), every 3 weeks (Q3W) for up to 35 treatments (approximately 2 years). Eligible participants who stopped the initial course of pembrolizumab with Stable Disease (SD) or better but progressed after discontinuation may have been able to initiate a second course of pembrolizumab for up to an additional 17 trial treatments (up to approximately 1 additional year) at the investigator's discretion.	

Primary: Objective Response Rate (ORR) According to Response Evaluation Criteria for Solid Tumors version 1.1 (RECIST 1.1) Assessed by Blinded Independent Central Review (BICR)

End point title	Objective Response Rate (ORR) According to Response Evaluation Criteria for Solid Tumors version 1.1 (RECIST 1.1) Assessed by Blinded Independent Central Review (BICR) ^[1]
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End point description:

ORR was defined as the percentage of participants 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 modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. The percentage of participants who experienced a CR or PR based on modified RECIST 1.1 was reported per protocol for the first course of treatment. All allocated participants who received at least 1 dose of study treatment were analysed.

End point type	Primary
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End point timeframe:

Up to approximately 28 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 statistical analyses were planned for this endpoint.

End point values	Pembrolizumab 200 mg			
Subject group type	Reporting group			
Number of subjects analysed	121			
Units: percentage of participants				
number (confidence interval 95%)	9.9 (5.2 to 16.7)			

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)
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End point description:

An AE was defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which did not necessarily have to have a causal relationship with this treatment. An AE could therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to

the medicinal product or protocol-specified procedure. Any worsening of a pre-existing condition that was temporally associated with the use of the Sponsor's product, was also an adverse event. The number of participants who experienced ≥ 1 AE was reported per protocol for the first course of treatment. All allocated participants who received at least 1 dose of study treatment were analysed.

End point type	Secondary
End point timeframe:	
Up to approximately 59 months	

End point values	Pembrolizumab 200 mg			
Subject group type	Reporting group			
Number of subjects analysed	121			
Units: Participants	116			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants that Discontinued Study Treatment due to an AE

End point title	Number of Participants that Discontinued Study Treatment due to an AE
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End point description:

An AE was defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which did not necessarily have to have a causal relationship with this treatment. An AE could therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening of a pre-existing condition that was temporally associated with the use of the Sponsor's product, was also an adverse event. The number of participants that discontinued study treatment due to an AE was reported per protocol for the first course of treatment. All allocated participants who received at least 1 dose of study treatment were analysed.

End point type	Secondary
End point timeframe:	
Up to approximately 24 months	

End point values	Pembrolizumab 200 mg			
Subject group type	Reporting group			
Number of subjects analysed	121			
Units: Participants	14			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) According to RECIST 1.1 Assessed by BICR

End point title	Duration of Response (DOR) According to RECIST 1.1 Assessed by BICR
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End point description:

For participants who demonstrated a confirmed CR (disappearance of all target lesions) or PR ($\geq 30\%$ decrease in the sum of diameters of target lesions) 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 $\geq 20\%$ increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also have demonstrated an absolute increase of ≥ 5 mm. The appearance of ≥ 1 new lesions was also considered PD. DOR assessments were based on BICR with confirmation. DOR per RECIST 1.1 for all participants who experienced a confirmed CR or PR was reported per protocol for the first course of treatment. All allocated participants who received at least 1 dose of study treatment and who experienced a confirmed CR or confirmed PR were analysed; 1 participant was excluded from DOR analysis based on a BICR re-read of prior scans after the primary analysis database lock

End point type	Secondary
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End point timeframe:

Up to approximately 67 months

End point values	Pembrolizumab 200 mg			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: Months				
median (full range (min-max))	19.7 (2.1 to 60.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) According to RECIST 1.1 Assessed by BICR

End point title	Progression Free Survival (PFS) According to RECIST 1.1 Assessed by BICR
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End point description:

PFS was defined as the time from first day of study treatment to the first documented PD or death due to any cause, whichever occurred first. Per RECIST 1.1, PD was defined as $\geq 20\%$ increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also have demonstrated an absolute increase of ≥ 5 mm. Note: The appearance of ≥ 1 new lesions was also considered PD. PFS as assessed by blinded independent central review per RECIST 1.1 was reported per protocol for the first course of treatment. All allocated participants who received at least 1 dose of study treatment were analysed.

End point type	Secondary
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End point timeframe:

Up to approximately 67 months

End point values	Pembrolizumab 200 mg			
Subject group type	Reporting group			
Number of subjects analysed	121			
Units: Months				
median (confidence interval 95%)	2.0 (1.9 to 2.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
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End point description:

OS was defined as the time from first day of study treatment to death due to any cause. Participants without documented death at the time of the final analysis were censored at the date of the last follow-up. OS was reported per protocol for the first course of treatment. All allocated participants who received at least 1 dose of study treatment were analysed.

End point type	Secondary
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End point timeframe:

Up to approximately 67 months

End point values	Pembrolizumab 200 mg			
Subject group type	Reporting group			
Number of subjects analysed	121			
Units: Months				
median (confidence interval 95%)	5.8 (4.5 to 7.2)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 67 months

Adverse event reporting additional description:

Deaths (all-causes) includes all allocated participants. Serious and Other AEs include all allocated participants who received ≥ 1 dose of study drug. Per protocol, MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" unrelated to drug were excluded as AEs.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.1
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Reporting groups

Reporting group title	Pembrolizumab 200 mg First Course
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Reporting group description:

Participants received pembrolizumab 200 mg IV Q3W for up to 35 treatments (approximately 2 years).

Reporting group title	Pembrolizumab 200 mg Second Course
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Reporting group description:

Eligible participants who stopped the initial course of pembrolizumab (200 mg IV Q3W for up to 35 treatments [approximately 2 years]) with SD or better but progressed after discontinuation initiated a second course of pembrolizumab at the investigator's discretion for up to an additional 17 trial treatments (up to approximately 1 additional year).

Serious adverse events	Pembrolizumab 200 mg First Course	Pembrolizumab 200 mg Second Course	
Total subjects affected by serious adverse events			
subjects affected / exposed	47 / 121 (38.84%)	0 / 1 (0.00%)	
number of deaths (all causes)	116	0	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour necrosis			
subjects affected / exposed	1 / 121 (0.83%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 121 (0.83%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			

subjects affected / exposed	1 / 121 (0.83%)	0 / 1 (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			
Malaise			
subjects affected / exposed	1 / 121 (0.83%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 121 (0.83%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Choking			
subjects affected / exposed	1 / 121 (0.83%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 121 (0.83%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 121 (0.83%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 121 (0.83%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			

subjects affected / exposed	3 / 121 (2.48%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 121 (0.83%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 121 (0.83%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 121 (0.83%)	0 / 1 (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	2 / 121 (1.65%)	0 / 1 (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			
Infusion related reaction			
subjects affected / exposed	1 / 121 (0.83%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury			
subjects affected / exposed	1 / 121 (0.83%)	0 / 1 (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 / 121 (0.83%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Congenital, familial and genetic disorders			
Tracheo-oesophageal fistula			
subjects affected / exposed	1 / 121 (0.83%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 121 (1.65%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 121 (0.83%)	0 / 1 (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			
Cerebrovascular accident			
subjects affected / exposed	1 / 121 (0.83%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 121 (0.83%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 121 (0.83%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 121 (0.83%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			

subjects affected / exposed	1 / 121 (0.83%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal pseudo-obstruction			
subjects affected / exposed	1 / 121 (0.83%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 121 (0.83%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 121 (0.83%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal stenosis			
subjects affected / exposed	2 / 121 (1.65%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Odynophagia			
subjects affected / exposed	1 / 121 (0.83%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 121 (0.83%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 121 (0.83%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	1 / 121 (0.83%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary obstruction			
subjects affected / exposed	1 / 121 (0.83%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	4 / 121 (3.31%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephritis			
subjects affected / exposed	1 / 121 (0.83%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 121 (0.83%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hypopituitarism			
subjects affected / exposed	2 / 121 (1.65%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	1 / 121 (0.83%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed	1 / 121 (0.83%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 121 (0.83%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 121 (0.83%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	16 / 121 (13.22%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	1 / 17	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	5 / 121 (4.13%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Sepsis			
subjects affected / exposed	1 / 121 (0.83%)	0 / 1 (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			
Decreased appetite			
subjects affected / exposed	1 / 121 (0.83%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	2 / 121 (1.65%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			

subjects affected / exposed	1 / 121 (0.83%)	0 / 1 (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 / 121 (0.83%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	1 / 121 (0.83%)	0 / 1 (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	Pembrolizumab 200 mg First Course	Pembrolizumab 200 mg Second Course	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	107 / 121 (88.43%)	1 / 1 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 121 (2.48%)	1 / 1 (100.00%)	
occurrences (all)	4	1	
Jugular vein thrombosis			
subjects affected / exposed	0 / 121 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	9 / 121 (7.44%)	0 / 1 (0.00%)	
occurrences (all)	10	0	
Fatigue			
subjects affected / exposed	34 / 121 (28.10%)	0 / 1 (0.00%)	
occurrences (all)	37	0	
Oedema peripheral			
subjects affected / exposed	10 / 121 (8.26%)	0 / 1 (0.00%)	
occurrences (all)	11	0	
Pain			

subjects affected / exposed	0 / 121 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	8 / 121 (6.61%)	1 / 1 (100.00%)	
occurrences (all)	13	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	24 / 121 (19.83%)	1 / 1 (100.00%)	
occurrences (all)	26	1	
Dyspnoea			
subjects affected / exposed	16 / 121 (13.22%)	0 / 1 (0.00%)	
occurrences (all)	19	0	
Epistaxis			
subjects affected / exposed	0 / 121 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Nasal congestion			
subjects affected / exposed	0 / 121 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	10 / 121 (8.26%)	0 / 1 (0.00%)	
occurrences (all)	10	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	12 / 121 (9.92%)	0 / 1 (0.00%)	
occurrences (all)	13	0	
Aspartate aminotransferase increased			
subjects affected / exposed	13 / 121 (10.74%)	0 / 1 (0.00%)	
occurrences (all)	14	0	
Blood alkaline phosphatase increased			
subjects affected / exposed	10 / 121 (8.26%)	0 / 1 (0.00%)	
occurrences (all)	11	0	
Weight decreased			
subjects affected / exposed	7 / 121 (5.79%)	0 / 1 (0.00%)	
occurrences (all)	8	0	
Blood bilirubin increased			

subjects affected / exposed occurrences (all)	9 / 121 (7.44%) 9	0 / 1 (0.00%) 0	
Nervous system disorders Neuropathy peripheral subjects affected / exposed occurrences (all)	7 / 121 (5.79%) 7	0 / 1 (0.00%) 0	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	18 / 121 (14.88%) 22	0 / 1 (0.00%) 0	
Ear and labyrinth disorders Deafness neurosensory subjects affected / exposed occurrences (all) Ear pain subjects affected / exposed occurrences (all)	0 / 121 (0.00%) 0 1 / 121 (0.83%) 1	1 / 1 (100.00%) 1 1 / 1 (100.00%) 1	
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Dry mouth subjects affected / exposed occurrences (all) Dysphagia subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Oral pain	9 / 121 (7.44%) 9 23 / 121 (19.01%) 24 18 / 121 (14.88%) 22 7 / 121 (5.79%) 7 8 / 121 (6.61%) 8 22 / 121 (18.18%) 26	0 / 1 (0.00%) 0 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0	

subjects affected / exposed occurrences (all)	3 / 121 (2.48%) 3	1 / 1 (100.00%) 1	
Vomiting subjects affected / exposed occurrences (all)	19 / 121 (15.70%) 25	0 / 1 (0.00%) 0	
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	13 / 121 (10.74%) 13	1 / 1 (100.00%) 1	
Rash subjects affected / exposed occurrences (all)	10 / 121 (8.26%) 13	0 / 1 (0.00%) 0	
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	11 / 121 (9.09%) 13	0 / 1 (0.00%) 0	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	8 / 121 (6.61%) 13	1 / 1 (100.00%) 1	
Back pain subjects affected / exposed occurrences (all)	11 / 121 (9.09%) 12	0 / 1 (0.00%) 0	
Myalgia subjects affected / exposed occurrences (all)	8 / 121 (6.61%) 8	1 / 1 (100.00%) 1	
Pain in extremity subjects affected / exposed occurrences (all)	5 / 121 (4.13%) 6	1 / 1 (100.00%) 1	
Rotator cuff syndrome subjects affected / exposed occurrences (all)	0 / 121 (0.00%) 0	1 / 1 (100.00%) 1	
Infections and infestations Pneumonia subjects affected / exposed occurrences (all)	9 / 121 (7.44%) 9	0 / 1 (0.00%) 0	

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	23 / 121 (19.01%)	0 / 1 (0.00%)	
occurrences (all)	23	0	
Hypokalaemia			
subjects affected / exposed	7 / 121 (5.79%)	0 / 1 (0.00%)	
occurrences (all)	10	0	
Hyponatraemia			
subjects affected / exposed	7 / 121 (5.79%)	0 / 1 (0.00%)	
occurrences (all)	8	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 December 2016	The major change of Amendment (AM) 2 was to indicate pre-specified Gene Expression Profile (GEP) cutoffs, instead of deriving the cut-offs from the MK-3475-180 data.
29 December 2017	Major changes of Amendment AM 4 included adding guidelines for the management of myocarditis based upon health authority feedback and removing the Pharmacokinetic and Anti-Drug Antibody collections at the 30-day Safety Follow up visit.
22 October 2021	Major changes of Amendment AM 6 included updating the criteria for early trial termination and clarifying the concomitant use of COVID-19 vaccines.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported