Clinical trial results:
A Multicenter, Open-label, Phase 2 Trial to Assess the Efficacy and Safety of Lenvatinib (E7080/MK-7902) in Combination with Pembrolizumab (MK-3475) in Participants with Advanced Melanoma Previously Exposed to an Anti-PD-1/L1 Agent (LEAP-004)

Summary

EudraCT number	2018-002518-10
Trial protocol	SE ES
Global end of trial date	11 October 2023

Results information

Result version number	v1 (current)
This version publication date	06 October 2024
First version publication date	06 October 2024

Trial information

Trial identification

Sponsor protocol code	7902-004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03776136
WHO universal trial number (UTN)	-
Other trial identifiers	MSD: LEAP-004, Eisai Protocol Number: E7080-G000-225

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@msd.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@msd.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	11 October 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 October 2023
Global end of trial reached?	Yes
Global end of trial date	11 October 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study will evaluate the safety and efficacy of combination therapy of lenvatinib (E7080/MK-7902) and pembrolizumab following approximately 2 years of pembrolizumab therapy and approximately 2 years or more lenvatinib therapy in adult participants with unresectable or advanced melanoma who have been exposed to anti-programmed cell death ligand 1 (PD-1/L1) agents approved for unresectable or metastatic melanoma. No statistical hypothesis will be tested in this study.

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	30 January 2019
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: 19
Country: Number of subjects enrolled	Canada: 21
Country: Number of subjects enrolled	Spain: 36
Country: Number of subjects enrolled	Sweden: 14
Country: Number of subjects enrolled	United States: 13
Worldwide total number of subjects	103
EEA total number of subjects	50

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)	58
From 65 to 84 years	44
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Participants with unresectable or metastatic melanoma previously exposed to an anti-PD-1/L1 agent were recruited into the study.

Pre-assignment

Screening details:

Of 139 participants screened, a total of 103 participants were allocated into the study.

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	Lenvatinib + Pembrolizumab

Arm description:

Participants received lenvatinib 20 mg orally once a day (QD) plus pembrolizumab 200 mg by intravenous (IV) infusion on Day 1 of each 21-day cycle (Q3W). Pembrolizumab was administered for up to 35 cycles (approximately 24 months). Lenvatinib was administered until progressive disease or unacceptable toxicity.

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

Dosage and administration details:

200 mg intravenously (IV) on Day 1 of each 21-day cycle (Q3W) for up to 35 cycles (up to ~2 years).

Investigational medicinal product name	Lenvatinib
Investigational medicinal product code	
Other name	MK-7902, E7080, LENVIMA™
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

20 mg orally once a day (QD) during each 21-day cycle.

Number of subjects in period 1	Lenvatinib + Pembrolizumab
Started	103
Treated	103
Completed	0
Not completed	103
Consent withdrawn by subject	3
Death	85
Sponsor Decision	15

Baseline characteristics

Reporting groups	
Reporting group title	Lenvatinib + Pembrolizumab
Reporting group description:	
Participants received lenvatinib 20 mg orally once a day (QD) plus pembrolizumab 200 mg by intravenous (IV) infusion on Day 1 of each 21-day cycle (Q3W). Pembrolizumab was administered for up to 35 cycles (approximately 24 months). Lenvatinib was administered until progressive disease or unacceptable toxicity.	

Reporting group values	Lenvatinib + Pembrolizumab	Total	
Number of subjects	103	103	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	58	58	
From 65-84 years	44	44	
85 years and over	1	1	
Age Continuous Units: Years			
arithmetic mean	60.7		
standard deviation	± 13.4	-	
Sex: Female, Male Units: Participants			
Female	48	48	
Male	55	55	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	3	3	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	1	1	
White	98	98	
More than one race	1	1	
Unknown or Not Reported	0	0	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	1	
Not Hispanic or Latino	100	100	
Unknown or Not Reported	2	2	

End points

End points reporting groups

Reporting group title	Lenvatinib + Pembrolizumab

Reporting group description:

Participants received lenvatinib 20 mg orally once a day (QD) plus pembrolizumab 200 mg by intravenous (IV) infusion on Day 1 of each 21-day cycle (Q3W). Pembrolizumab was administered for up to 35 cycles (approximately 24 months). Lenvatinib was administered until progressive disease or unacceptable toxicity.

Primary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)[1]

End point description:

ORR was defined as the percentage of participants in the analysis population who have a confirmed Complete Response (CR: disappearance of all lesions) or a Partial Response (PR: ≥30% decrease in the sum of target lesion diameters without progression in other lesions) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) by Blinded Independent Central Review (BICR). Per protocol, RECIST 1.1 was modified to allow up to 10 target lesions total (up to 5 per organ). ORR is reported here for all participants who received at least one dose of study intervention.

End point type	Primary

End point timeframe:

Up to approximately 55 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: Per protocol, no statistical analysis were planned for this endpoint.

End point values	Lenvatinib + Pembrolizumab			
Subject group type	Reporting group			
Number of subjects analysed	103			
Units: Percentage of Participants				
number (confidence interval 95%)	21.4 (13.9 to 30.5)			

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 day of study intervention to the first documented progressive disease (PD) per RECIST 1.1 by BICR, or death from any cause, whichever occurred first. Per protocol, RECIST 1.1 was modified to allow up to 10 target lesions total (up to 5 per organ). PFS was calculated using the nonparametric Kaplan-Meier method; participants who did not experience a PFS event were censored at the last disease assessment, or the last assessment before new anticancer treatment if new treatment was initiated. PFS is reported here for all participants who received at least one dose of study intervention.

End point type	Secondary

End point timeframe:

Up to approximately 55 months

End point values	Lenvatinib + Pembrolizumab			
Subject group type	Reporting group			
Number of subjects analysed	103			
Units: Months				
median (confidence interval 95%)	4.2 (3.5 to 6.3)			

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 Complete Response (CR: disappearance of all lesions) or Partial Response (PR: ≥30% decrease in the sum of target lesion diameters without progression in other lesions) per RECIST 1.1, DOR was defined as the time from first documented CR or PR until progressive disease (PD) or death from any cause, whichever occurs first. Per protocol, RECIST 1.1 was modified to allow up to 10 target lesions total (up to 5 per organ). DOR was calculated using the nonparametric Kaplan-Meier method for censored data. DOR is reported here for all participants who received at least one dose of study intervention, and who experienced a confirmed CR or PR.

End point type	Secondary

End point timeframe:

Up to approximately 55 months

End point values	Lenvatinib + Pembrolizumab			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: Months				
median (full range (min-max))	8.5 (3.2 to 40.8)			

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 the first day of study intervention 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 calculated using the nonparametric Kaplan-Meier method. OS is reported here for all participants who received at least one dose of study intervention.

End point type	Secondary

End point timeframe:

Up to approximately 55 months

End point values	Lenvatinib + Pembrolizumab			
Subject group type	Reporting group			
Number of subjects analysed	103			
Units: Months				
median (confidence interval 95%)	14.0 (10.8 to 18.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration Time Curve of Lenvatinib From Time 0 to Infinity (AUC 0-inf)

End point title	Area Under the Concentration Time Curve of Lenvatinib From Time 0 to Infinity (AUC 0-inf)

End point description:

AUC0-inf was defined as the area under the concentration-time curve from time zero extrapolated to infinity. Plasma blood samples collected at specified timepoints, were used to estimate AUC0-inf following Lenvatinib and Pembrolizumab administration. Based on the lenvatinib plasma concentration data obtained on Cycle 1 Day 1, Cycle 1 Day 15, and Cycle 2 Day 1, a protocol specified population PK analysis was performed to characterize the steady state AUC0-inf of lenvatinib when co-administered with pembrolizumab. AUC0-inf is reported here for all participants who received at least one dose of study intervention, and had data available for AUC0-inf.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1: 0.5 to 4 hours and 6 to 10 hours postdose; Cycle 1 Day 15: Predose and 2 to 12 hours postdose; Cycle 2 Day 1: Predose, 0.5 to 4 hours, and 6 to 10 hours post-dose (each cycle =21 days)

End point values	Lenvatinib + Pembrolizumab			
Subject group type	Reporting group			
Number of subjects analysed	103			
Units: ng*hr/mL				
geometric mean (geometric coefficient of variation)	3005 (± 39.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Experience At Least One Adverse Event (AE)

End point title	Number of Participants Who Experience At Least One Adverse Event (AE)

End point description:

An AE was any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. An AE could therefore have been any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention. The number of participants who experienced an AE is presented here for all participants who received at least one dose of study intervention.

End point type	Secondary

End point timeframe:

Up to approximately 55 months

End point values	Lenvatinib + Pembrolizumab			
Subject group type	Reporting group			
Number of subjects analysed	103			
Units: Participants	102			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Discontinue Study Treatment Due to an AE

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

End point description:

An AE was any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. An AE could therefore have been any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention. The number of participants who discontinued study treatment due to an AE is presented here for all participants who received at least one dose of study intervention.

End point type	Secondary

End point timeframe:

Up to approximately 48 months

End point values	Lenvatinib + Pembrolizumab			
Subject group type	Reporting group			
Number of subjects analysed	103			
Units: Participants	15			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 55 months

Adverse event reporting additional description:

All-cause mortality and adverse events (AEs): all participants who received ≥1 dose of treatment. Per protocol, disease progression was not considered an AE unless considered related to study drug. Thus MedDRA preferred terms Neoplasm progression, Malignant neoplasm progression and Disease progression not related to study drug are excluded as AEs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	Lenvatinib + Pembrolizumab

Reporting group description: -

Serious adverse events	Lenvatinib + Pembrolizumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	48 / 103 (46.60%)		
number of deaths (all causes)	86		
number of deaths resulting from adverse events	4		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour haemorrhage			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Basal cell carcinoma			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cancer pain			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malignant melanoma			

subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 103 (1.94%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 103 (1.94%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Non-cardiac chest pain			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malaise			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	2 / 103 (1.94%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			

subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Disorientation			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Confusional state			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Platelet count decreased			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Injury, poisoning and procedural complications			
Wound secretion			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Muscle rupture			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Femoral neck fracture			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Supraventricular tachycardia			

subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bradycardia			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute coronary syndrome			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Horner's syndrome			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	2 / 103 (1.94%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Immune thrombocytopenia			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			

Nausea			
subjects affected / exposed	2 / 103 (1.94%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Melaena			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intra-abdominal haematoma			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Enteritis			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	5 / 103 (4.85%)		
occurrences causally related to treatment / all	4 / 5		
deaths causally related to treatment / all	0 / 0		
Abdominal pain upper			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	2 / 103 (1.94%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Colitis			

subjects affected / exposed	1 / 103 (0.97%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Proctitis				
subjects affected / exposed	1 / 103 (0.97%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Proctalgia				
subjects affected / exposed	1 / 103 (0.97%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	1 / 103 (0.97%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Oesophagitis				
subjects affected / exposed	1 / 103 (0.97%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholecystitis chronic				
subjects affected / exposed	1 / 103 (0.97%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholecystitis acute				
subjects affected / exposed	2 / 103 (1.94%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Biliary obstruction				
subjects affected / exposed	1 / 103 (0.97%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Biliary colic				

subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Acute kidney injury			
subjects affected / exposed	2 / 103 (1.94%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Urinary retention			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Fistula			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Biliary sepsis			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Appendicitis			

subjects affected / exposed	1 / 103 (0.97%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Escherichia bacteraemia				
subjects affected / exposed	1 / 103 (0.97%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	2 / 103 (1.94%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Groin abscess				
subjects affected / exposed	1 / 103 (0.97%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pelvic abscess				
subjects affected / exposed	1 / 103 (0.97%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Wound infection				
subjects affected / exposed	1 / 103 (0.97%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Viral upper respiratory tract infection				
subjects affected / exposed	1 / 103 (0.97%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	4 / 103 (3.88%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 2			
Pneumonia aspiration				

subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Failure to thrive			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diabetic ketoacidosis			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperkalaemia			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	3 / 103 (2.91%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Malnutrition			
subjects affected / exposed	1 / 103 (0.97%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Lenvatinib + Pembrolizumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	101 / 103 (98.06%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	58 / 103 (56.31%)		
occurrences (all)	88		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	31 / 103 (30.10%)		
occurrences (all)	59		
Fatigue			
subjects affected / exposed	36 / 103 (34.95%)		
occurrences (all)	44		
Mucosal inflammation			
subjects affected / exposed	18 / 103 (17.48%)		
occurrences (all)	30		
Oedema peripheral			
subjects affected / exposed	6 / 103 (5.83%)		
occurrences (all)	6		
Pyrexia			
subjects affected / exposed	20 / 103 (19.42%)		
occurrences (all)	23		
Respiratory, thoracic and mediastinal disorders			
Aphonia			
subjects affected / exposed	7 / 103 (6.80%)		
occurrences (all)	10		
Oropharyngeal pain			
subjects affected / exposed	9 / 103 (8.74%)		
occurrences (all)	9		
Epistaxis			
subjects affected / exposed	6 / 103 (5.83%)		
occurrences (all)	8		

Dyspnoea			
subjects affected / exposed	8 / 103 (7.77%)		
occurrences (all)	8		
Dysphonia			
subjects affected / exposed	22 / 103 (21.36%)		
occurrences (all)	24		
Cough			
subjects affected / exposed	12 / 103 (11.65%)		
occurrences (all)	14		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	11 / 103 (10.68%)		
occurrences (all)	12		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	16 / 103 (15.53%)		
occurrences (all)	19		
Lipase increased			
subjects affected / exposed	14 / 103 (13.59%)		
occurrences (all)	14		
Haemoglobin decreased			
subjects affected / exposed	7 / 103 (6.80%)		
occurrences (all)	10		
Blood thyroid stimulating hormone increased			
subjects affected / exposed	9 / 103 (8.74%)		
occurrences (all)	12		
Blood magnesium decreased			
subjects affected / exposed	6 / 103 (5.83%)		
occurrences (all)	18		
Blood alkaline phosphatase increased			
subjects affected / exposed	7 / 103 (6.80%)		
occurrences (all)	9		
Aspartate aminotransferase increased			
subjects affected / exposed	13 / 103 (12.62%)		
occurrences (all)	18		
Amylase increased			

subjects affected / exposed	10 / 103 (9.71%)		
occurrences (all)	15		
Neutrophil count decreased			
subjects affected / exposed	6 / 103 (5.83%)		
occurrences (all)	6		
Weight decreased			
subjects affected / exposed	23 / 103 (22.33%)		
occurrences (all)	25		
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	12 / 103 (11.65%)		
occurrences (all)	15		
Headache			
subjects affected / exposed	29 / 103 (28.16%)		
occurrences (all)	56		
Dizziness			
subjects affected / exposed	18 / 103 (17.48%)		
occurrences (all)	22		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	14 / 103 (13.59%)		
occurrences (all)	15		
Neutropenia			
subjects affected / exposed	7 / 103 (6.80%)		
occurrences (all)	9		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	19 / 103 (18.45%)		
occurrences (all)	27		
Gastrooesophageal reflux disease			
subjects affected / exposed	12 / 103 (11.65%)		
occurrences (all)	13		
Nausea			
subjects affected / exposed	46 / 103 (44.66%)		
occurrences (all)	64		
Stomatitis			

subjects affected / exposed	14 / 103 (13.59%)		
occurrences (all)	15		
Toothache			
subjects affected / exposed	6 / 103 (5.83%)		
occurrences (all)	6		
Vomiting			
subjects affected / exposed	28 / 103 (27.18%)		
occurrences (all)	51		
Dry mouth			
subjects affected / exposed	15 / 103 (14.56%)		
occurrences (all)	18		
Abdominal pain upper			
subjects affected / exposed	9 / 103 (8.74%)		
occurrences (all)	13		
Diarrhoea			
subjects affected / exposed	50 / 103 (48.54%)		
occurrences (all)	123		
Constipation			
subjects affected / exposed	32 / 103 (31.07%)		
occurrences (all)	39		
Skin and subcutaneous tissue disorders			
Vitiligo			
subjects affected / exposed	6 / 103 (5.83%)		
occurrences (all)	6		
Rash			
subjects affected / exposed	12 / 103 (11.65%)		
occurrences (all)	15		
Pruritus			
subjects affected / exposed	18 / 103 (17.48%)		
occurrences (all)	19		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	7 / 103 (6.80%)		
occurrences (all)	8		
Dry skin			

subjects affected / exposed occurrences (all)	11 / 103 (10.68%) 11		
Renal and urinary disorders Proteinuria subjects affected / exposed occurrences (all)	 23 / 103 (22.33%) 34		
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	 37 / 103 (35.92%) 39		
Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all) Muscular weakness subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	 15 / 103 (14.56%) 18 6 / 103 (5.83%) 6 20 / 103 (19.42%) 24 27 / 103 (26.21%) 39 11 / 103 (10.68%) 12		
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	 6 / 103 (5.83%) 6 15 / 103 (14.56%) 17		
Metabolism and nutrition disorders Hypophosphataemia			

subjects affected / exposed	6 / 103 (5.83%)		
occurrences (all)	7		
Hyponatraemia			
subjects affected / exposed	9 / 103 (8.74%)		
occurrences (all)	9		
Hypomagnesaemia			
subjects affected / exposed	13 / 103 (12.62%)		
occurrences (all)	23		
Hypokalaemia			
subjects affected / exposed	10 / 103 (9.71%)		
occurrences (all)	15		
Decreased appetite			
subjects affected / exposed	42 / 103 (40.78%)		
occurrences (all)	58		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 January 2019	Amendment 1: To address agency comments associated with the potential for a clinical hold; amendment required to proceed with first site-ready milestone.
05 June 2019	Amendment 2: To address feedback from regulatory authority and add MK-7902 program-level updates.
17 June 2020	Amendment 3: To clarify Adverse Event Safety Follow-up timelines, to clarify allowed concomitant medications, and to add MK-7902 program-level updates.
05 October 2021	Amendment 4: To update the pembrolizumab dose modification and toxicity management guidelines for immune-related adverse events (irAEs) and table, to add MK-7902 program-level updates.
29 September 2022	Amendment 5: Sponsor underwent an entity name change and update to the address. Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported