Clinical trial results:
A Phase 3 Multicenter, Randomized, Double-blinded, Active-controlled, Clinical Study to Evaluate the Safety and Efficacy of Lenvatinib (E7080/MK-7902) in Combination with Pembrolizumab (MK-3475) Versus Lenvatinib in First-line Therapy of Participants with Advanced Hepatocellular Carcinoma (LEAP-002)

Summary

EudraCT number	2018-002983-26
Trial protocol	GB IE ES DE PL IT
Global end of trial date	24 September 2024

Results information

Result version number	v1 (current)
This version publication date	23 October 2025
First version publication date	23 October 2025

Trial information

Trial identification

Sponsor protocol code	7902-002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03713593
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@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	21 June 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 June 2022
Global end of trial reached?	Yes
Global end of trial date	24 September 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the safety and efficacy of lenvatinib (E7080/MK-7902) in combination with pembrolizumab (MK-3745) versus lenvatinib in combination with placebo as first-line therapy for the treatment of advanced hepatocellular carcinoma in adult participants.
The primary hypotheses of this study are that lenvatinib plus pembrolizumab is superior to lenvatinib plus placebo with respect to progression-free survival (PFS) and overall survival (OS).

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	31 December 2018
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: 11
Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	Chile: 15
Country: Number of subjects enrolled	China: 150
Country: Number of subjects enrolled	Colombia: 19
Country: Number of subjects enrolled	France: 109
Country: Number of subjects enrolled	Germany: 31
Country: Number of subjects enrolled	Ireland: 5
Country: Number of subjects enrolled	Italy: 43
Country: Number of subjects enrolled	Japan: 80
Country: Number of subjects enrolled	Korea, Republic of: 50
Country: Number of subjects enrolled	Mexico: 39
Country: Number of subjects enrolled	New Zealand: 6
Country: Number of subjects enrolled	Poland: 27
Country: Number of subjects enrolled	Russian Federation: 31
Country: Number of subjects enrolled	Spain: 17
Country: Number of subjects enrolled	Taiwan: 31
Country: Number of subjects enrolled	Thailand: 13

Country: Number of subjects enrolled	Türkiye: 31
Country: Number of subjects enrolled	United Kingdom: 25
Country: Number of subjects enrolled	United States: 54
Worldwide total number of subjects	794
EEA total number of subjects	232

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)	370
From 65 to 84 years	416
85 years and over	8

Subject disposition

Recruitment

Recruitment details:

Participants with a radiologically, histologically- or cytologically-confirmed diagnosis of hepatocellular carcinoma (HCC) were recruited into this study.

Pre-assignment

Screening details:

794 participants were randomly assigned in a 1:1 ratio to either combination therapy, Pembrolizumab+Lenvatinib, or Lenvatinib+Placebo, to assess the safety and efficacy of Lenvatinib in combination with Pembrolizumab versus Lenvatinib in first-line therapy of participants with advanced hepatocellular carcinoma

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Lenvatinib + Pembrolizumab

Arm description:

Participants received lenvatinib 12 mg (for participants with screening body weight ≥60 kg) or 8 mg (for participants with screening body weight <60 kg) 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	MK-3475 KEYTRUDA®
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

200 mg via intravenous (IV) infusion on Day 1 of each 3-week cycle (Q3W) for up to 35 administrations (up to approximately 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:

8 mg via oral capsule once daily (QD) on Days 1-21 of each 3-week cycle until progressive disease or unacceptable toxicity

Arm title	Lenvatinib + Placebo

Arm description:

Participants received lenvatinib 12 mg (for participants with screening body weight ≥60 kg) or 8 mg (for participants with screening body weight <60 kg) orally QD plus saline placebo by IV infusion on Day 1 Q3W. Saline placebo was administered for up to 35 cycles (approximately 24 months). Lenvatinib was administered until progressive disease or unacceptable toxicity.

Arm type	Active comparator

Investigational medicinal product name	Placebo matching pembrolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

0 mg via IV infusion on Day 1 of each Q3W for up to 35 administrations (up to approximately 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:

8 mg via oral capsule once daily (QD) on Days 1-21 of each 3-week cycle until progressive disease or unacceptable toxicity

Number of subjects in period 1	Lenvatinib + Pembrolizumab	Lenvatinib + Placebo
Started	395	399
Completed	0	0
Not completed	395	399
Consent withdrawn by subject	6	8
Death	314	349
Sponsor Decision	73	41
Lost to follow-up	2	1

Baseline characteristics

Reporting groups	
Reporting group title	Lenvatinib + Pembrolizumab
Reporting group description:	
Participants received lenvatinib 12 mg (for participants with screening body weight ≥60 kg) or 8 mg (for participants with screening body weight <60 kg) 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 title	Lenvatinib + Placebo
Reporting group description:	
Participants received lenvatinib 12 mg (for participants with screening body weight ≥60 kg) or 8 mg (for participants with screening body weight <60 kg) orally QD plus saline placebo by IV infusion on Day 1 Q3W. Saline placebo was administered for up to 35 cycles (approximately 24 months). Lenvatinib was administered until progressive disease or unacceptable toxicity.	

Reporting group values	Lenvatinib + Pembrolizumab	Lenvatinib + Placebo	Total
Number of subjects	395	399	794
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous Units: Years			
arithmetic mean	64.2	64.1	
standard deviation	± 10.9	± 12.1	-
Sex: Female, Male Units: Participants			
Female	78	72	150
Male	317	327	644
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	13	8	21
Asian	172	173	345
Native Hawaiian or Other Pacific Islander	2	0	2
Black or African American	5	8	13
White	173	172	345
More than one race	12	10	22
Unknown or Not Reported	18	28	46
Ethnicity (NIH/OMB)			

Units: Subjects			
Hispanic or Latino	48	41	89
Not Hispanic or Latino	334	349	683
Unknown or Not Reported	13	9	22
Eastern Cooperative Oncology Group (ECOG) Performance Status			
Randomization of participants in the study was stratified by an ECOG Performance Status of 0 (Fully active, able to carry on all pre-disease performance without restriction) or 1 (Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature) or 2 (Ambulatory but unable to work). The number of participants with missing ECOG performance status is indicated for each treatment arm.			
Units: Subjects			
ECOG = 0	267	271	538
ECOG = 1	127	126	253
ECOG = 2	1	0	1
Missing	0	2	2
Geographic Region			
Randomization of participants in this study was stratified by geographic region of the enrolling site (Asia without Japan versus Japan and Western regions).			
Units: Subjects			
Asia without Japan	121	123	244
Japan and Western regions	274	276	550

End points

End points reporting groups

Reporting group title	Lenvatinib + Pembrolizumab

Reporting group description:

Participants received lenvatinib 12 mg (for participants with screening body weight ≥60 kg) or 8 mg (for participants with screening body weight <60 kg) 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 title	Lenvatinib + Placebo

Reporting group description:

Participants received lenvatinib 12 mg (for participants with screening body weight ≥60 kg) or 8 mg (for participants with screening body weight <60 kg) orally QD plus saline placebo by IV infusion on Day 1 Q3W. Saline placebo was administered for up to 35 cycles (approximately 24 months). Lenvatinib was administered until progressive disease or unacceptable toxicity.

Primary: 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 the date of the first documentation of disease progression, as determined by blinded independent central review (BICR) per RECIST 1.1 or death due to any cause (whichever occurred first). Disease progression was defined as at least 20 percent (%) increase (including an absolute increase of at least 5 millimeter [mm]) in the sum of diameter of target lesions, taking as reference the smallest sum and/or unequivocal progression of existing non-target lesions and/or appearance of 1 or more new lesions. PFS was estimated and analyzed using Kaplan-Meier method.

End point type	Primary

End point timeframe:

Up to approximately 41 months

End point values	Lenvatinib + Pembrolizumab	Lenvatinib + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	395	399		
Units: Months				
median (confidence interval 95%)	8.2 (6.3 to 8.3)	8.1 (6.3 to 8.3)		

Statistical analyses

Statistical analysis title	Hazard Ratio (HR)
Comparison groups	Lenvatinib + Pembrolizumab v Lenvatinib + Placebo

Number of subjects included in analysis	794
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.834
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.712
upper limit	0.978

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description:	
OS was defined as the time from randomization until death from any cause	
End point type	Primary
End point timeframe:	
Up to approximately 41 months	

End point values	Lenvatinib + Pembrolizumab	Lenvatinib + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	395	399		
Units: Months				
median (confidence interval 95%)	21.2 (19.0 to 23.6)	19.0 (17.2 to 21.7)		

Statistical analyses

Statistical analysis title	Hazard Ratio (HR)
Comparison groups	Lenvatinib + Pembrolizumab v Lenvatinib + Placebo
Number of subjects included in analysis	794
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0227
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.708
upper limit	0.997

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 determined by disease assessment and is defined as the time from the first documented evidence of a response of CR or PR, per RECIST 1.1 as assessed by BICR, until the first documented disease progression or death due to any cause, whichever occurred first. RECIST 1.1 has been modified for this study to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

End point type	Secondary

End point timeframe:

Up to approximately 41 months

End point values	Lenvatinib + Pembrolizumab	Lenvatinib + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	70		
Units: Months				
median (full range (min-max))	4.1 (1.3 to 25.3)	4.0 (0.3 to 18.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: 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)

End point description:

ORR was defined as the percentage of participants who have a confirmed complete response (CR: disappearance of all target lesions) or partial response (PR: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters) per RECIST 1.1 as assessed by BICR. RECIST 1.1 has been modified for this study to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

End point type	Secondary

End point timeframe:

Up to approximately 41 months

End point values	Lenvatinib + Pembrolizumab	Lenvatinib + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	395	399		
Units: Percentage of Participants				
number (confidence interval 95%)	26.1 (21.8 to 30.7)	17.5 (13.9 to 21.6)		

Statistical analyses

Statistical analysis title	Difference in percentage
Comparison groups	Lenvatinib + Pembrolizumab v Lenvatinib + Placebo
Number of subjects included in analysis	794
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in percentage
Point estimate	8.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.8
upper limit	14.2

Secondary: Disease Control Rate (DCR) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)

End point title	Disease Control Rate (DCR) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)

End point description:

DCR was defined as the percentage of participants who have a best overall response of CR, PR, or stable disease (SD) per RECIST 1.1 as assessed by BICR. SD must be achieved at ≥6 weeks after randomization to be considered best overall response. RECIST 1.1 has been modified for this study to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

End point type	Secondary

End point timeframe:

Up to approximately 41 months

End point values	Lenvatinib + Pembrolizumab	Lenvatinib + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	395	399		
Units: Percentage of Participants				
number (confidence interval 95%)	81.3 (77.1 to 85.0)	78.4 (74.1 to 82.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS) per Modified Response Evaluation Criteria in Solid Tumors (mRECIST)

End point title	Progression-free Survival (PFS) per Modified Response Evaluation Criteria in Solid Tumors (mRECIST)

End point description:

PFS was defined as the time from the first dose of study intervention to the first documented progressive disease (PD) per mRECIST by BICR or death due to any cause, whichever occurred first. mRECIST for HCC allowed evaluation of treatment effects that were not reflected in simple total size changes of lesions. Per mRECIST, PD was defined as an increase of at least 20% in the sum of diameters (SODs) of viable (enhancing) target lesions, taking as reference the smallest SODs of viable (enhancing) target lesions recorded since the treatment started.

End point type	Secondary

End point timeframe:

Up to approximately 41 months

End point values	Lenvatinib + Pembrolizumab	Lenvatinib + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	395	399		
Units: Months				
median (confidence interval 95%)	8.4 (8.2 to 10.2)	8.1 (6.5 to 8.3)		

Statistical analyses

Statistical analysis title	Hazard Ratio (HR)
Comparison groups	Lenvatinib + Pembrolizumab v Lenvatinib + Placebo
Number of subjects included in analysis	794
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	0.94

Secondary: Objective Response Rate (ORR) per Modified Response Evaluation Criteria in Solid Tumors (mRECIST)

End point title	Objective Response Rate (ORR) per Modified Response Evaluation Criteria in Solid Tumors (mRECIST)

End point description:

ORR wass defined as the percentage of participants who have a confirmed complete response (CR: disappearance of any intratumoral arterial enhancement in all target lesions) or partial response (PR: at least a 30% decrease in the sum of diameters of viable [enhancement in the arterial phase] target lesions, taking as reference the baseline sum of the diameters of target lesions) per mRECIST as assessed by BICR. mRECIST for hepatocellular carcinoma evaluates lesions within the liver parenchyma showing increased contrast enhancement in the arterial phase. A maximum of 10 target lesions and a maximum of 5 target lesions per organ were followed.

End point type	Secondary

End point timeframe:

Up to approximately 41 months

End point values	Lenvatinib + Pembrolizumab	Lenvatinib + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	395	399		
Units: Percentage of Participants				
number (confidence interval 95%)	40.8 (35.9 to 45.8)	34.1 (29.4 to 39.0)		

Statistical analyses

Statistical analysis title	Difference in percentage
Comparison groups	Lenvatinib + Pembrolizumab v Lenvatinib + Placebo
Number of subjects included in analysis	794
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in percentage
Point estimate	6.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	13.4

Secondary: Time to Disease Progression (TTP) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)

End point title	Time to Disease Progression (TTP) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)

End point description:

TTP was defined as the time from randomization to the first documented disease progression per RECIST 1.1 as assessed by BICR. RECIST 1.1 was modified for this study to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ were followed.

End point type	Secondary

End point timeframe:

Up to approximately 41 months

End point values	Lenvatinib + Pembrolizumab	Lenvatinib + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	395	399		
Units: Months				
median (confidence interval 95%)	8.3 (8.1 to 10.3)	8.2 (7.0 to 8.4)		

Statistical analyses

Statistical analysis title	Hazard Ratio (HR)
Comparison groups	Lenvatinib + Pembrolizumab v Lenvatinib + Placebo
Number of subjects included in analysis	794
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	0.93

Secondary: Duration of Response (DOR) per Modified Response Evaluation Criteria in Solid Tumors (mRECIST)

End point title	Duration of Response (DOR) per Modified Response Evaluation Criteria in Solid Tumors (mRECIST)

End point description:

DOR was determined by disease assessment and is defined as the time from the first documented evidence of a response of CR or PR, per mRECIST as assessed by BICR, until the first documented disease progression or death due to any cause, whichever occurs first. mRECIST for hepatocellular carcinoma evaluates lesions within the liver parenchyma showing increased contrast enhancement in the arterial phase. A maximum of 10 target lesions and a maximum of 5 target lesions per organ were followed.

End point type	Secondary

End point timeframe:

Up to approximately 41 months

End point values	Lenvatinib + Pembrolizumab	Lenvatinib + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151	136		
Units: Months				
median (full range (min-max))	2.1 (1.2 to 16.6)	2.1 (0.2 to 14.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR) per Modified Response Evaluation Criteria in Solid Tumors (mRECIST)

End point title	Disease Control Rate (DCR) per Modified Response Evaluation Criteria in Solid Tumors (mRECIST)

End point description:

DCR was defined as the percentage of participants who have a best overall response of CR, PR, or SD per mRECIST as assessed by BICR. mRECIST for hepatocellular carcinoma evaluates lesions within the liver parenchyma showing increased contrast enhancement in the arterial phase. SD must be achieved at ≥6 weeks after randomization to be considered best overall response. A maximum of 10 target lesions and a maximum of 5 target lesions per organ were followed.

End point type	Secondary

End point timeframe:

Up to approximately 41 months

End point values	Lenvatinib + Pembrolizumab	Lenvatinib + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	395	399		
Units: Percentage of Participants				
number (confidence interval 95%)	84.3 (80.3 to 87.7)	83.2 (79.2 to 86.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Experienced an Immune-related Adverse Event (irAE) of Clinical Interest

End point title	Number of Participants Who Experienced an Immune-related Adverse Event (irAE) of Clinical Interest

End point description:

Number of participants who experienced an AE representing an immunologic etiology and considered to be causally related to drug exposure

End point type	Secondary

End point timeframe:

Up to approximately 41 months

End point values	Lenvatinib + Pembrolizumab	Lenvatinib + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	395	395		
Units: Participants	210	184		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Disease Progression (TTP) per Modified Response Evaluation Criteria in Solid Tumors (mRECIST)

End point title	Time to Disease Progression (TTP) per Modified Response Evaluation Criteria in Solid Tumors (mRECIST)

End point description:

TTP was defined as the time from randomization to the first documented disease progression per mRECIST as assessed by BICR. mRECIST for hepatocellular carcinoma evaluates lesions within the liver parenchyma showing increased contrast enhancement in the arterial phase. A maximum of 10 target lesions and a maximum of 5 target lesions per organ were followed.

End point type	Secondary

End point timeframe:

Up to approximately 41 months

End point values	Lenvatinib + Pembrolizumab	Lenvatinib + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	395	399		
Units: Months				
median (confidence interval 95%)	10.4 (8.5 to 11.7)	8.3 (8.1 to 8.9)		

Statistical analyses

Statistical analysis title	Hazard Ratio (HR)
Comparison groups	Lenvatinib + Pembrolizumab v Lenvatinib + Placebo
Number of subjects included in analysis	794
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.73

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	0.88

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:

Number of participants who experienced an AE defined as any unfavorable and unintended sign, symptom, disease, or worsening of preexisting condition temporally associated with study therapy and irrespective of causality to study treatment

End point type	Secondary

End point timeframe:

Up to approximately 68 months

End point values	Lenvatinib + Pembrolizumab	Lenvatinib + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	395	395		
Units: Participants	394	392		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Experienced an Serious Adverse Event (SAE)

End point title	Number of Participants Who Experienced an Serious Adverse Event (SAE)

End point description:

Number of participants who experienced a SAE defined as an AE that resulted in death, was life threatening, resulting in persistent or significant disability or incapacity, resulting in or prolonged a hospitalization, was a congenital anomaly or birth defect, was a cancer, was associated with an overdose, or was another important medical event

End point type	Secondary

End point timeframe:

Up to approximately 68 months

End point values	Lenvatinib + Pembrolizumab	Lenvatinib + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	395	395		
Units: Participants	185	159		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Experienced an Hepatic Event of Clinical Interest (HECI)

End point title	Number of Participants Who Experienced an Hepatic Event of Clinical Interest (HECI)

End point description:

Number of participants who experienced a hepatic ECI not due to disease progression as judged by the investigator.

End point type	Secondary

End point timeframe:

Up to approximately 68 months

End point values	Lenvatinib + Pembrolizumab	Lenvatinib + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	395	395		
Units: Participants	71	77		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Discontinued Study Drug Due to an Adverse Event

End point title	Number of Participants Who Discontinued Study Drug Due to an Adverse Event

End point description:

Number of participants who discontinued study treatment due to an AE

End point type	Secondary

End point timeframe:

Up to approximately 68 months

End point values	Lenvatinib + Pembrolizumab	Lenvatinib + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	395	395		
Units: Participants	51	41		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to ~ 68 months	
Adverse event reporting additional description:	
AE additional description	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups	
Reporting group title	Lenvatinib + Placebo
Reporting group description:	
Participants received lenvatinib 12 mg (for participants with screening body weight ≥60 kg) or 8 mg (for participants with screening body weight <60 kg) orally QD plus saline placebo by IV infusion on Day 1 Q3W. Saline placebo was administered for up to 35 cycles (approximately 24 months). Lenvatinib was administered until progressive disease or unacceptable toxicity.	
Reporting group title	Lenvatinib + Pembrolizumab
Reporting group description:	
Participants received lenvatinib 12 mg (for participants with screening body weight ≥60 kg) or 8 mg (for participants with screening body weight <60 kg) 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.	

Serious adverse events	Lenvatinib + Placebo	Lenvatinib + Pembrolizumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	159 / 395 (40.25%)	185 / 395 (46.84%)	
number of deaths (all causes)	352	314	
number of deaths resulting from adverse events	21	29	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 395 (0.25%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver carcinoma ruptured			

subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Malignant neoplasm of unknown primary site			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 395 (0.25%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin squamous cell carcinoma recurrent			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	2 / 395 (0.51%)	3 / 395 (0.76%)	
occurrences causally related to treatment / all	1 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Vasculitis			
subjects affected / exposed	1 / 395 (0.25%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive emergency			

subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	2 / 395 (0.51%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	2 / 395 (0.51%)	3 / 395 (0.76%)	
occurrences causally related to treatment / all	1 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic aneurysm			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (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			
Drowning			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Asthenia			
subjects affected / exposed	0 / 395 (0.00%)	3 / 395 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	3 / 395 (0.76%)	5 / 395 (1.27%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 3	0 / 5	
Fatigue			

subjects affected / exposed	2 / 395 (0.51%)	3 / 395 (0.76%)	
occurrences causally related to treatment / all	1 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 395 (0.00%)	7 / 395 (1.77%)	
occurrences causally related to treatment / all	0 / 0	3 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthermia malignant			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 395 (0.00%)	2 / 395 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Oedema peripheral			
subjects affected / exposed	2 / 395 (0.51%)	2 / 395 (0.51%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	4 / 395 (1.01%)	3 / 395 (0.76%)	
occurrences causally related to treatment / all	3 / 5	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stent-graft endoleak			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			

subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Scrotal inflammation			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatitis			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (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			
Oropharyngeal spasm			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract congestion			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Idiopathic pulmonary fibrosis			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Hiccups			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	2 / 395 (0.51%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 395 (0.00%)	4 / 395 (1.01%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic respiratory failure			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary embolism			

subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Confusional state			
subjects affected / exposed	1 / 395 (0.25%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
False positive investigation result			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood thyroid stimulating hormone decreased			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood glucose decreased			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood creatinine increased			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	1 / 395 (0.25%)	5 / 395 (1.27%)	
occurrences causally related to treatment / all	0 / 1	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 395 (0.25%)	3 / 395 (0.76%)	
occurrences causally related to treatment / all	1 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amylase increased			
subjects affected / exposed	0 / 395 (0.00%)	2 / 395 (0.51%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	1 / 395 (0.25%)	4 / 395 (1.01%)	
occurrences causally related to treatment / all	1 / 1	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	2 / 395 (0.51%)	2 / 395 (0.51%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin T increased			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 395 (0.25%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Contusion			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (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	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament rupture			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint injury			

subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	1 / 395 (0.25%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrioventricular block complete			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 395 (0.00%)	2 / 395 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 395 (0.25%)	2 / 395 (0.51%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			

subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	2 / 395 (0.51%)	3 / 395 (0.76%)	
occurrences causally related to treatment / all	2 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Atrioventricular block second degree			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	2 / 395 (0.51%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Coronary artery disease			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	2 / 395 (0.51%)	3 / 395 (0.76%)	
occurrences causally related to treatment / all	0 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial injury			

subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocarditis			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus node dysfunction			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 395 (0.25%)	2 / 395 (0.51%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	
Depressed level of consciousness			

subjects affected / exposed	0 / 395 (0.00%)	3 / 395 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolic stroke			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			
subjects affected / exposed	11 / 395 (2.78%)	21 / 395 (5.32%)	
occurrences causally related to treatment / all	6 / 12	14 / 27	
deaths causally related to treatment / all	0 / 0	2 / 2	
Ischaemic stroke			
subjects affected / exposed	1 / 395 (0.25%)	2 / 395 (0.51%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myasthenia gravis			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ruptured cerebral aneurysm			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 395 (0.00%)	2 / 395 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient global amnesia			

subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Agranulocytosis			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	1 / 395 (0.25%)	5 / 395 (1.27%)	
occurrences causally related to treatment / all	0 / 1	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune thrombocytopenia			
subjects affected / exposed	0 / 395 (0.00%)	2 / 395 (0.51%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Diabetic retinopathy			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glaucoma			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pterygium			

subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal distension			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal hernia			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	4 / 395 (1.01%)	8 / 395 (2.03%)	
occurrences causally related to treatment / all	3 / 4	3 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	10 / 395 (2.53%)	5 / 395 (1.27%)	
occurrences causally related to treatment / all	3 / 10	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			

subjects affected / exposed	1 / 395 (0.25%)	2 / 395 (0.51%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 395 (0.25%)	2 / 395 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	5 / 395 (1.27%)	13 / 395 (3.29%)	
occurrences causally related to treatment / all	5 / 5	13 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer perforation, obstructive			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	1 / 395 (0.25%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesenteric vein thrombosis			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			

subjects affected / exposed	1 / 395 (0.25%)	2 / 395 (0.51%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	1 / 395 (0.25%)	2 / 395 (0.51%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric varices haemorrhage			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 395 (0.51%)	3 / 395 (0.76%)	
occurrences causally related to treatment / all	1 / 2	2 / 3	
deaths causally related to treatment / all	1 / 1	1 / 1	
Gastrointestinal inflammation			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoperitoneum			
subjects affected / exposed	2 / 395 (0.51%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 395 (0.25%)	3 / 395 (0.76%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			

subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	2 / 395 (0.51%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	1 / 395 (0.25%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mechanical ileus			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			

subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 395 (0.25%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal ulcer haemorrhage			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Oesophageal varices haemorrhage			
subjects affected / exposed	5 / 395 (1.27%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	3 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 395 (0.00%)	2 / 395 (0.51%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	2 / 395 (0.51%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumatosis intestinalis			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal perforation			

subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	4 / 395 (1.01%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	5 / 5	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varices oesophageal			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 395 (0.00%)	2 / 395 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal haemorrhage			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary obstruction			
subjects affected / exposed	2 / 395 (0.51%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stone			

subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	2 / 395 (0.51%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis acute			
subjects affected / exposed	1 / 395 (0.25%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis chronic			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cirrhosis			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	8 / 395 (2.03%)	4 / 395 (1.01%)	
occurrences causally related to treatment / all	1 / 8	1 / 5	
deaths causally related to treatment / all	0 / 5	0 / 2	
Immune-mediated hepatitis			
subjects affected / exposed	1 / 395 (0.25%)	2 / 395 (0.51%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic haemorrhage			

subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic necrosis			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic pain			
subjects affected / exposed	1 / 395 (0.25%)	2 / 395 (0.51%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatorenal syndrome			
subjects affected / exposed	2 / 395 (0.51%)	2 / 395 (0.51%)	
occurrences causally related to treatment / all	1 / 2	1 / 3	
deaths causally related to treatment / all	1 / 2	1 / 2	
Hepatic function abnormal			
subjects affected / exposed	3 / 395 (0.76%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal vein thrombosis			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver injury			

subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psoriasis			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pemphigoid			
subjects affected / exposed	0 / 395 (0.00%)	2 / 395 (0.51%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parapsoriasis			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lichenoid keratosis			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hidradenitis			

subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Henoch-Schonlein purpura			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	2 / 395 (0.51%)	3 / 395 (0.76%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nephritis			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrotic syndrome			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal tubular necrosis			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal infarct			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			

subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prerenal failure			
subjects affected / exposed	1 / 395 (0.25%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 395 (0.00%)	2 / 395 (0.51%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthyroidism			
subjects affected / exposed	1 / 395 (0.25%)	2 / 395 (0.51%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophysitis			
subjects affected / exposed	0 / 395 (0.00%)	2 / 395 (0.51%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroiditis			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Arthralgia			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	2 / 395 (0.51%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tenosynovitis			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 395 (0.25%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fistula			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc degeneration			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			

subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteolysis			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw			
subjects affected / exposed	2 / 395 (0.51%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cytomegalovirus colitis			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal infection			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal sepsis			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	1 / 395 (0.25%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anorectal infection			

subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 395 (0.25%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	3 / 395 (0.76%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary tract infection			
subjects affected / exposed	2 / 395 (0.51%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bronchitis			
subjects affected / exposed	3 / 395 (0.76%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	3 / 395 (0.76%)	5 / 395 (1.27%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 2	
COVID-19 pneumonia			
subjects affected / exposed	1 / 395 (0.25%)	3 / 395 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			

subjects affected / exposed	2 / 395 (0.51%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cryptococcosis			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungaemia			

subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 395 (0.25%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious pleural effusion			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine infection			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	1 / 395 (0.25%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periodontitis			

subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	2 / 395 (0.51%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis bacterial			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy bacterial			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	7 / 395 (1.77%)	8 / 395 (2.03%)	
occurrences causally related to treatment / all	1 / 7	2 / 8	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	3 / 395 (0.76%)	3 / 395 (0.76%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 2	
Salmonellosis			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			

subjects affected / exposed	2 / 395 (0.51%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatic abscess			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia klebsiella			
subjects affected / exposed	0 / 395 (0.00%)	2 / 395 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia cryptococcal			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord infection			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal sepsis			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			

subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 395 (0.51%)	4 / 395 (1.01%)	
occurrences causally related to treatment / all	1 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 395 (0.51%)	3 / 395 (0.76%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 395 (0.76%)	2 / 395 (0.51%)	
occurrences causally related to treatment / all	2 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	4 / 395 (1.01%)	2 / 395 (0.51%)	
occurrences causally related to treatment / all	2 / 4	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			

subjects affected / exposed	0 / 395 (0.00%)	2 / 395 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 395 (0.00%)	2 / 395 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 1 diabetes mellitus			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	0 / 395 (0.00%)	2 / 395 (0.51%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hyponatraemia			
subjects affected / exposed	2 / 395 (0.51%)	2 / 395 (0.51%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			

subjects affected / exposed	1 / 395 (0.25%)	3 / 395 (0.76%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 395 (0.00%)	3 / 395 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoalbuminaemia			
subjects affected / exposed	1 / 395 (0.25%)	0 / 395 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypervolaemia			
subjects affected / exposed	0 / 395 (0.00%)	1 / 395 (0.25%)	
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	Lenvatinib + Placebo	Lenvatinib + Pembrolizumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	388 / 395 (98.23%)	390 / 395 (98.73%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	200 / 395 (50.63%)	180 / 395 (45.57%)	
occurrences (all)	258	248	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	61 / 395 (15.44%)	73 / 395 (18.48%)	
occurrences (all)	85	90	
Fatigue			
subjects affected / exposed	98 / 395 (24.81%)	126 / 395 (31.90%)	
occurrences (all)	124	148	
Malaise			

subjects affected / exposed	30 / 395 (7.59%)	20 / 395 (5.06%)	
occurrences (all)	35	24	
Mucosal inflammation			
subjects affected / exposed	19 / 395 (4.81%)	25 / 395 (6.33%)	
occurrences (all)	25	30	
Oedema peripheral			
subjects affected / exposed	54 / 395 (13.67%)	63 / 395 (15.95%)	
occurrences (all)	68	86	
Pyrexia			
subjects affected / exposed	45 / 395 (11.39%)	48 / 395 (12.15%)	
occurrences (all)	66	60	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	29 / 395 (7.34%)	25 / 395 (6.33%)	
occurrences (all)	42	28	
Dyspnoea			
subjects affected / exposed	24 / 395 (6.08%)	44 / 395 (11.14%)	
occurrences (all)	32	47	
Dysphonia			
subjects affected / exposed	79 / 395 (20.00%)	83 / 395 (21.01%)	
occurrences (all)	92	94	
Cough			
subjects affected / exposed	43 / 395 (10.89%)	55 / 395 (13.92%)	
occurrences (all)	49	66	
Oropharyngeal pain			
subjects affected / exposed	15 / 395 (3.80%)	23 / 395 (5.82%)	
occurrences (all)	17	24	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	43 / 395 (10.89%)	35 / 395 (8.86%)	
occurrences (all)	49	40	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	89 / 395 (22.53%)	93 / 395 (23.54%)	
occurrences (all)	155	162	
Gamma-glutamyltransferase increased			

subjects affected / exposed	56 / 395 (14.18%)	65 / 395 (16.46%)	
occurrences (all)	72	78	
Blood creatinine increased			
subjects affected / exposed	25 / 395 (6.33%)	39 / 395 (9.87%)	
occurrences (all)	41	60	
Blood bilirubin increased			
subjects affected / exposed	108 / 395 (27.34%)	101 / 395 (25.57%)	
occurrences (all)	216	222	
Blood alkaline phosphatase increased			
subjects affected / exposed	35 / 395 (8.86%)	50 / 395 (12.66%)	
occurrences (all)	54	64	
Aspartate aminotransferase increased			
subjects affected / exposed	105 / 395 (26.58%)	117 / 395 (29.62%)	
occurrences (all)	179	195	
Amylase increased			
subjects affected / exposed	18 / 395 (4.56%)	40 / 395 (10.13%)	
occurrences (all)	30	64	
Lipase increased			
subjects affected / exposed	37 / 395 (9.37%)	57 / 395 (14.43%)	
occurrences (all)	59	79	
Neutrophil count decreased			
subjects affected / exposed	39 / 395 (9.87%)	34 / 395 (8.61%)	
occurrences (all)	85	73	
Platelet count decreased			
subjects affected / exposed	110 / 395 (27.85%)	101 / 395 (25.57%)	
occurrences (all)	198	170	
Weight decreased			
subjects affected / exposed	90 / 395 (22.78%)	121 / 395 (30.63%)	
occurrences (all)	105	139	
White blood cell count decreased			
subjects affected / exposed	45 / 395 (11.39%)	29 / 395 (7.34%)	
occurrences (all)	105	75	
Nervous system disorders			
Headache			

subjects affected / exposed	43 / 395 (10.89%)	51 / 395 (12.91%)	
occurrences (all)	58	67	
Dysgeusia			
subjects affected / exposed	19 / 395 (4.81%)	22 / 395 (5.57%)	
occurrences (all)	21	26	
Dizziness			
subjects affected / exposed	28 / 395 (7.09%)	26 / 395 (6.58%)	
occurrences (all)	30	30	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	64 / 395 (16.20%)	51 / 395 (12.91%)	
occurrences (all)	88	61	
Neutropenia			
subjects affected / exposed	22 / 395 (5.57%)	19 / 395 (4.81%)	
occurrences (all)	38	54	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	73 / 395 (18.48%)	67 / 395 (16.96%)	
occurrences (all)	81	81	
Diarrhoea			
subjects affected / exposed	167 / 395 (42.28%)	187 / 395 (47.34%)	
occurrences (all)	352	359	
Dry mouth			
subjects affected / exposed	14 / 395 (3.54%)	20 / 395 (5.06%)	
occurrences (all)	14	20	
Dyspepsia			
subjects affected / exposed	14 / 395 (3.54%)	33 / 395 (8.35%)	
occurrences (all)	18	41	
Nausea			
subjects affected / exposed	82 / 395 (20.76%)	89 / 395 (22.53%)	
occurrences (all)	120	123	
Stomatitis			
subjects affected / exposed	35 / 395 (8.86%)	41 / 395 (10.38%)	
occurrences (all)	47	55	
Toothache			

subjects affected / exposed	18 / 395 (4.56%)	24 / 395 (6.08%)	
occurrences (all)	23	28	
Vomiting			
subjects affected / exposed	61 / 395 (15.44%)	54 / 395 (13.67%)	
occurrences (all)	93	93	
Ascites			
subjects affected / exposed	29 / 395 (7.34%)	28 / 395 (7.09%)	
occurrences (all)	34	35	
Abdominal pain upper			
subjects affected / exposed	40 / 395 (10.13%)	46 / 395 (11.65%)	
occurrences (all)	53	52	
Abdominal pain			
subjects affected / exposed	74 / 395 (18.73%)	74 / 395 (18.73%)	
occurrences (all)	91	88	
Abdominal distension			
subjects affected / exposed	18 / 395 (4.56%)	27 / 395 (6.84%)	
occurrences (all)	20	33	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	35 / 395 (8.86%)	63 / 395 (15.95%)	
occurrences (all)	46	79	
Pruritus			
subjects affected / exposed	44 / 395 (11.14%)	67 / 395 (16.96%)	
occurrences (all)	57	79	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	125 / 395 (31.65%)	133 / 395 (33.67%)	
occurrences (all)	141	155	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	24 / 395 (6.08%)	27 / 395 (6.84%)	
occurrences (all)	55	43	
Proteinuria			
subjects affected / exposed	153 / 395 (38.73%)	136 / 395 (34.43%)	
occurrences (all)	268	280	
Endocrine disorders			

Hyperthyroidism			
subjects affected / exposed	15 / 395 (3.80%)	31 / 395 (7.85%)	
occurrences (all)	16	32	
Hypothyroidism			
subjects affected / exposed	159 / 395 (40.25%)	167 / 395 (42.28%)	
occurrences (all)	202	207	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	23 / 395 (5.82%)	19 / 395 (4.81%)	
occurrences (all)	27	22	
Myalgia			
subjects affected / exposed	14 / 395 (3.54%)	25 / 395 (6.33%)	
occurrences (all)	15	27	
Back pain			
subjects affected / exposed	43 / 395 (10.89%)	60 / 395 (15.19%)	
occurrences (all)	49	72	
Arthralgia			
subjects affected / exposed	77 / 395 (19.49%)	89 / 395 (22.53%)	
occurrences (all)	93	114	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	14 / 395 (3.54%)	20 / 395 (5.06%)	
occurrences (all)	16	27	
Urinary tract infection			
subjects affected / exposed	42 / 395 (10.63%)	35 / 395 (8.86%)	
occurrences (all)	65	48	
Metabolism and nutrition disorders			
Hypophosphataemia			
subjects affected / exposed	23 / 395 (5.82%)	19 / 395 (4.81%)	
occurrences (all)	43	24	
Hyponatraemia			
subjects affected / exposed	39 / 395 (9.87%)	43 / 395 (10.89%)	
occurrences (all)	64	69	
Hypomagnesaemia			
subjects affected / exposed	28 / 395 (7.09%)	27 / 395 (6.84%)	
occurrences (all)	56	46	

Hypokalaemia			
subjects affected / exposed	36 / 395 (9.11%)	39 / 395 (9.87%)	
occurrences (all)	60	75	
Decreased appetite			
subjects affected / exposed	120 / 395 (30.38%)	146 / 395 (36.96%)	
occurrences (all)	167	183	
Hyperglycaemia			
subjects affected / exposed	25 / 395 (6.33%)	24 / 395 (6.08%)	
occurrences (all)	46	33	
Hyperkalaemia			
subjects affected / exposed	20 / 395 (5.06%)	14 / 395 (3.54%)	
occurrences (all)	26	22	
Hypertriglyceridaemia			
subjects affected / exposed	31 / 395 (7.85%)	24 / 395 (6.08%)	
occurrences (all)	64	51	
Hypoalbuminaemia			
subjects affected / exposed	61 / 395 (15.44%)	62 / 395 (15.70%)	
occurrences (all)	99	85	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 May 2019	The major changes for AM1 was to address feedback from regulatory authorities and align with MK-7902 program standard updates.
11 May 2021	The major changes for AM2 was to remove pharmacokinetic (PK) objective and update pembrolizumab dose modification table.
08 December 2022	The major changes for AM3 was to space out clinic visits to every 6 weeks and imaging scans to every 12 weeks.
17 October 2023	The major changes for AM4 was to add Study extension.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported