



Clinical trial results:

A Phase 3 Randomized Study of Lenvatinib in Combination with Pembrolizumab Versus Standard of Care in Participants with Metastatic Colorectal Cancer Who Have Received and Progressed On or After or Became Intolerant to Prior Treatment

Summary

EudraCT number	2020-004289-20
Trial protocol	DE DK
Global end of trial date	27 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	7902-017
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04776148
WHO universal trial number (UTN)	-
Other trial identifiers	Merck Protocol Number: MK-7902-017, Merck: LEAP-017, Eisai Protocol Number: E7080-G000-325, jRCT: 2031200453

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme LLC
Sponsor organisation address	126 East Lincoln Avenue, P.O. Box 2000, Rahway, NJ, United States, 07065
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@msd.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@msd.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 September 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 September 2024
Global end of trial reached?	Yes
Global end of trial date	27 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 assess the safety and efficacy of lenvatinib (MK-7902/E7080) in combination with pembrolizumab (MK-3475) in participants with metastatic colorectal cancer. The study will also compare lenvatinib plus pembrolizumab with the standard of care treatment of regorafenib and TAS-102 (trifluridine and tipiracil hydrochloride). The primary study hypothesis is that lenvatinib plus pembrolizumab is superior to standard of care with respect to overall survival.

The Global portion, or Global Cohort, will include all participants who are enrolled during the Global enrollment period and will be the primary analysis population for the study. The China Cohort will include both participants enrolled in China for the Global Cohort plus those participants enrolled in China as part of the China extension enrollment period.

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	29 March 2021
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	Argentina: 21
Country: Number of subjects enrolled	Australia: 24
Country: Number of subjects enrolled	Canada: 25
Country: Number of subjects enrolled	China: 100
Country: Number of subjects enrolled	Denmark: 25
Country: Number of subjects enrolled	Germany: 17
Country: Number of subjects enrolled	Israel: 36
Country: Number of subjects enrolled	Japan: 63
Country: Number of subjects enrolled	Korea, Republic of: 41
Country: Number of subjects enrolled	Russian Federation: 22
Country: Number of subjects enrolled	Spain: 49
Country: Number of subjects enrolled	Taiwan: 33
Country: Number of subjects enrolled	Türkiye: 50
Country: Number of subjects enrolled	United Kingdom: 25
Country: Number of subjects enrolled	United States: 32

Worldwide total number of subjects	563
EEA total number of subjects	91

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)	395
From 65 to 84 years	167
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

A total of 480 participants were enrolled in the Global Cohort, including 17 participants from China. An additional 83 participants were subsequently enrolled in the China extension, bringing the total number of participants in the China Cohort to 100 and the overall study population to 563.

Pre-assignment

Screening details:

The protocol specified non-alpha controlled final analyses for the China Cohort was conducted with a 27-Sep 2024 data cutoff, after the protocol-specified final analyses of the Global Cohort was completed on 20-Feb-2023.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Lenvatinib+pembrolizumab

Arm description:

Participants received pembrolizumab 400 mg via intravenous (IV) infusion on Day 1 of each 6-week (Q6W) Cycle for up to 18 cycles (up to approximately 2 years) PLUS lenvatinib 20 mg via oral capsule once daily until progressive disease.

Arm type	Experimental
Investigational medicinal product name	lenvatinib
Investigational medicinal product code	
Other name	MK-7902 E7080
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

oral capsule

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

Dosage and administration details:

IV infusion

Arm title	Standard of Care (SOC) treatment
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Arm description:

Participants received regorafenib 160 mg via oral tablet once daily on Days 1 through 21 of each 4-week cycle OR TAS-102 (trifluridine and tipiracil hydrochloride) 35 mg/m² via oral tablet twice a day on Days 1 through 5 and Days 8-12 of each 4-week cycle until progressive disease.

Arm type	Active comparator
Investigational medicinal product name	TAS-102 (trifluridine and tipiracil)
Investigational medicinal product code	
Other name	LONSURF®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

oral tablet

Investigational medicinal product name	regorafenib
Investigational medicinal product code	
Other name	STIVARGA® REGONIX®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

oral tablet

Number of subjects in period 1	Lenvatinib+pembrolizumab	Standard of Care (SOC) treatment
Started	282	281
Treated	279	277
Global Cohort Efficacy	241	239
China Cohort Efficacy	53	47
Global Cohort Safety	238	235
China Cohort Safety	53	47
Completed	0	0
Not completed	282	281
Adverse event, serious fatal	249	260
Consent withdrawn by subject	3	4
Withdrawal by Parent/Guardian	-	1
Sponsor Decision	30	15
Lost to follow-up	-	1

Baseline characteristics

Reporting groups

Reporting group title	Lenvatinib+pembrolizumab
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Reporting group description:

Participants received pembrolizumab 400 mg via intravenous (IV) infusion on Day 1 of each 6-week (Q6W) Cycle for up to 18 cycles (up to approximately 2 years) PLUS lenvatinib 20 mg via oral capsule once daily until progressive disease.

Reporting group title	Standard of Care (SOC) treatment
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Reporting group description:

Participants received regorafenib 160 mg via oral tablet once daily on Days 1 through 21 of each 4-week cycle OR TAS-102 (trifluridine and tipiracil hydrochloride) 35 mg/m² via oral tablet twice a day on Days 1 through 5 and Days 8-12 of each 4-week cycle until progressive disease.

Reporting group values	Lenvatinib+pembrolizumab	Standard of Care (SOC) treatment	Total
Number of subjects	282	281	563
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	199	196	395
From 65-84 years	82	85	167
85 years and over	1	0	1
Age Continuous Units: Years			
arithmetic mean	57.1	57.2	-
standard deviation	± 11.7	± 11.7	-
Sex: Female, Male Units: Participants			
Female	121	116	237
Male	161	165	326
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	122	123	245
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	5	3	8
White	152	152	304
More than one race	1	1	2
Unknown or Not Reported	2	2	4
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	26	13	39
Not Hispanic or Latino	255	267	522

Unknown or Not Reported	1	1	2
Presence of Liver Metastasis			
Number of participants with liver metastasis at baseline (Yes/No)			
Units: Subjects			
Yes	192	190	382
No metastasis at baseline	90	91	181

End points

End points reporting groups

Reporting group title	Lenvatinib+pembrolizumab
Reporting group description: Participants received pembrolizumab 400 mg via intravenous (IV) infusion on Day 1 of each 6-week (Q6W) Cycle for up to 18 cycles (up to approximately 2 years) PLUS lenvatinib 20 mg via oral capsule once daily until progressive disease.	
Reporting group title	Standard of Care (SOC) treatment
Reporting group description: Participants received regorafenib 160 mg via oral tablet once daily on Days 1 through 21 of each 4-week cycle OR TAS-102 (trifluridine and tipiracil hydrochloride) 35 mg/m ² via oral tablet twice a day on Days 1 through 5 and Days 8-12 of each 4-week cycle until progressive disease.	

Primary: Global Cohort: Overall Survival (OS)

End point title	Global Cohort: Overall Survival (OS)
End point description: OS was defined as the time from randomization to the date of death from any cause. OS is presented for all randomized participants in the Global Cohort. Per the supplemental Statistical Analysis Plan (sSAP), Final Analysis for the Global Cohort was performed with a data cut-off date of 20-Feb-2023.	
End point type	Primary
End point timeframe: Up to approximately 22 months (through sSAP pre-specified Final Analysis database cut-off date of 20-Feb-2023)	

End point values	Lenvatinib+pe mbrolizumab	Standard of Care (SOC) treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	241	239		
Units: Months				
median (confidence interval 95%)	9.8 (8.4 to 11.6)	9.3 (8.2 to 10.9)		

Statistical analyses

Statistical analysis title	Global OS comparison
Statistical analysis description: Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by presence of liver metastasis (Yes/No).	
Comparison groups	Lenvatinib+pembrolizumab v Standard of Care (SOC) treatment

Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0379 ^[1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1.02

Notes:

[1] - One-sided p-value based on log-rank test stratified by presence of liver metastasis.

Primary: China Cohort: Overall Survival (OS)

End point title	China Cohort: Overall Survival (OS)
End point description:	OS was defined as the time from randomization to the date of death from any cause. OS is presented for all randomized participants in the China Cohort. Per the sSAP, the China Cohort was evaluated for efficacy separately from the Global Cohort, with Final Analysis performed using a data cut-off of 27-Sep-2024.
End point type	Primary
End point timeframe:	Up to approximately 35 months (through sSAP pre-specified Final Analysis database cut-off date of 27-Sep-2024)

End point values	Lenvatinib+pembrolizumab	Standard of Care (SOC) treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	47		
Units: Months				
median (confidence interval 95%)	10.9 (8.8 to 16.5)	10.2 (6.1 to 12.7)		

Statistical analyses

Statistical analysis title	China OS comparison
Statistical analysis description:	Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
Comparison groups	Lenvatinib+pembrolizumab v Standard of Care (SOC) treatment

Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3574 ^[2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.42

Notes:

[2] - One-sided p-value based on log-rank test.

Secondary: Global Cohort: Progression Free Survival (PFS) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR)

End point title	Global Cohort: Progression Free Survival (PFS) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR)
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End point description:

PFS was defined as the time from date of randomization to the date of the first documentation of progressive disease (PD) or death from any cause, whichever occurs first. Per RECIST 1.1 modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, PD was defined as $\geq 20\%$ increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of ≥ 5 mm. Note: The appearance of one or more new lesions was also considered PD. PFS as assessed by BICR per modified RECIST 1.1 is presented for all randomized participants in the Global Cohort. Per the sSAP, Final Analysis for the Global Cohort was performed with a data cut-off date of 20-Feb-2023.

End point type	Secondary
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End point timeframe:

Up to approximately 22 months (through sSAP pre-specified Final Analysis database cut-off date of 20-Feb-2023)

End point values	Lenvatinib+pembrolizumab	Standard of Care (SOC) treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	241	239		
Units: Months				
median (confidence interval 95%)	3.8 (3.7 to 5.1)	3.3 (2.0 to 3.7)		

Statistical analyses

Statistical analysis title	Global PFS comparison
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Statistical analysis description:

Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by presence of liver metastasis (Yes/No).

Comparison groups	Lenvatinib+pembrolizumab v Standard of Care (SOC)
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	treatment
Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0003 ^[3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	0.85

Notes:

[3] - One-sided p-value based on log-rank test stratified by presence of liver metastasis.

Secondary: China Cohort: Progression Free Survival (PFS) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR)

End point title	China Cohort: Progression Free Survival (PFS) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR)
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End point description:

PFS was defined as the time from date of randomization to the date of the first documentation of progressive disease (PD) or death from any cause, whichever occurs first. Per RECIST 1.1 modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, PD was defined as $\geq 20\%$ increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of ≥ 5 mm. Note: The appearance of one or more new lesions was also considered PD. PFS as assessed by BICR per modified RECIST 1.1 is presented for all randomized participants in the China Cohort. Per the sSAP, the China Cohort was evaluated for efficacy separately from the Global Cohort, with Final Analysis performed using a data cut-off of 27-Sep-2024.

End point type	Secondary
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End point timeframe:

Up to approximately 35 months (through sSAP pre-specified Final Analysis database cut-off date of 27-Sep-2024)

End point values	Lenvatinib+pe mbrolizumab	Standard of Care (SOC) treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	47		
Units: Months				
median (confidence interval 95%)	3.7 (2.9 to 3.9)	2.4 (1.9 to 5.4)		

Statistical analyses

Statistical analysis title	China PFS comparison
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Statistical analysis description:

Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.

Comparison groups	Lenvatinib+pembrolizumab v Standard of Care (SOC)
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	treatment
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7421 ^[4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.15
Confidence interval	
level	Other: 85 %
sides	2-sided
lower limit	0.75
upper limit	1.77

Notes:

[4] - One-sided p-value based on log-rank test.

Secondary: Global Cohort: Objective Response Rate (ORR) per RECIST 1.1 as Assessed by BICR

End point title	Global Cohort: Objective Response Rate (ORR) per RECIST 1.1 as Assessed by BICR
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End point description:

ORR is defined as the percentage of participants in the analysis population who have a Complete Response (CR: Disappearance of all target lesions) or a Partial Response (PR: At least a 30% decrease in the sum of diameters of target lesions) per RECIST 1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. ORR per modified RECIST 1.1 assessed by BICR is presented for all randomized participants in the Global Cohort. Per the sSAP, Final Analysis for the Global Cohort was performed with a data cut-off date of 20-Feb-2023.

End point type	Secondary
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End point timeframe:

Up to approximately 22 months (through sSAP pre-specified Final Analysis database cut-off date of 20-Feb-2023)

End point values	Lenvatinib+pembrolizumab	Standard of Care (SOC) treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	241	239		
Units: Percentage of Participants				
number (confidence interval 95%)	10.4 (6.8 to 14.9)	1.7 (0.5 to 4.2)		

Statistical analyses

Statistical analysis title	Global ORR comparison
Comparison groups	Lenvatinib+pembrolizumab v Standard of Care (SOC) treatment

Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Chi-squared
Parameter estimate	Difference in Percentage vs. SOC
Point estimate	8.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.7
upper limit	13.5

Secondary: China Cohort: Objective Response Rate (ORR) per RECIST 1.1 as Assessed by BICR

End point title	China Cohort: Objective Response Rate (ORR) per RECIST 1.1 as Assessed by BICR
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End point description:

ORR is defined as the percentage of participants in the analysis population who have a Complete Response (CR: Disappearance of all target lesions) or a Partial Response (PR: At least a 30% decrease in the sum of diameters of target lesions) per RECIST 1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. ORR per modified RECIST 1.1 assessed by BICR is presented for all randomized participants in the Global Cohort. Per the sSAP, the China Cohort was evaluated for efficacy separately from the Global Cohort, with Final Analysis performed using a data cut-off of 27-Sep-2024.

End point type	Secondary
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End point timeframe:

Up to approximately 35 months (through sSAP pre-specified Final Analysis database cut-off date of 27-Sep-2024)

End point values	Lenvatinib+pembrolizumab	Standard of Care (SOC) treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	47		
Units: Percentage of Participants				
number (confidence interval 95%)	7.5 (2.1 to 18.2)	4.3 (0.5 to 14.5)		

Statistical analyses

Statistical analysis title	China ORR comparison
Comparison groups	Lenvatinib+pembrolizumab v Standard of Care (SOC) treatment

Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2456
Method	Chi-squared
Parameter estimate	Difference in Percentage vs. SOC
Point estimate	3.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.7
upper limit	14.3

Secondary: Global Cohort: Duration of Response (DOR) per RECIST 1.1 as Assessed by BICR

End point title	Global Cohort: Duration of Response (DOR) per RECIST 1.1 as Assessed by BICR
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End point description:

For participants who demonstrated CR (disappearance of all target lesions) or PR (at least a 30% decrease in the sum of diameters of target lesions), DOR is defined as the time from the first documented evidence of CR or PR until PD or death from any cause, whichever occurs first. Per RECIST 1.1 modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, or death from any cause. DOR as assessed by BICR per modified RECIST 1.1 is presented for all randomized participants in the Global Cohort. Values of 9999 indicate that the upper limit was not reached at time of data cut-off due to insufficient number of responding participants with relapse. Per the sSAP, Final Analysis for the Global Cohort was performed with a data cut-off date of 20-Feb-2023.

End point type	Secondary
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End point timeframe:

Up to approximately 22 months (through sSAP pre-specified Final Analysis database cut-off date of 20-Feb-2023)

End point values	Lenvatinib+pe mbrolizumab	Standard of Care (SOC) treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	4		
Units: Months				
median (confidence interval 95%)	11.1 (7.7 to 9999)	7.6 (6.0 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: China Cohort: Duration of Response (DOR) per RECIST 1.1 as Assessed by BICR

End point title	China Cohort: Duration of Response (DOR) per RECIST 1.1 as Assessed by BICR
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End point description:

For participants who demonstrated CR (disappearance of all target lesions) or PR (at least a 30% decrease in the sum of diameters of target lesions), DOR is defined as the time from the first documented evidence of CR or PR until PD or death from any cause, whichever occurs first. Per RECIST 1.1 modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, or death from any cause. DOR as assessed by BICR per modified RECIST 1.1 is presented for all randomized participants in the China Cohort. Values of 8888 indicate that the upper limit was not reached at time of data cut-off due to insufficient number of responding participants with relapse. A value of 9999 indicates that the median duration and upper limit not reached at time of data cut-off due to insufficient number of responding participants with relapse. Per the sSAP, the China Cohort was evaluated for efficacy separately from the Global Cohort.

End point type	Secondary
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End point timeframe:

Up to approximately 35 months (through sSAP pre-specified Final Analysis database cut-off date of 27-Sep-2024)

End point values	Lenvatinib+pe mbrolizumab	Standard of Care (SOC) treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	2		
Units: Months				
median (confidence interval 95%)	4.4 (3.5 to 8888)	9999 (9.1 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Global Cohort: Number of Participants Who Experience an Adverse Event (AE)

End point title	Global Cohort: Number of Participants Who Experience an Adverse Event (AE)
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End point description:

An adverse event is defined as any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention. All randomized participants in the Global Cohort who received at least one dose of study treatment were analyzed. Two participants randomized to pembrolizumab plus lenvatinib group were incorrectly treated with SOC; these participants were included in the SOC group for safety analyses. Per the sSAP, Final Analysis for the Global Cohort was performed with a data cut-off date of 20-Feb-2023.

End point type	Secondary
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End point timeframe:

Up to approximately 22 months (through sSAP pre-specified Final Analysis database cut-off date of 20-Feb-2023)

End point values	Lenvatinib+pe mbrolizumab	Standard of Care (SOC) treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	238	235		
Units: Participants	237	230		

Statistical analyses

No statistical analyses for this end point

Secondary: China Cohort: Number of Participants Who Experience an Adverse Event (AE)

End point title	China Cohort: Number of Participants Who Experience an Adverse Event (AE)
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End point description:

An adverse event is defined as any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention. All randomized participants in the China Cohort who received at least one dose of study treatment were analyzed. Per the sSAP, the China Cohort was evaluated for safety separately from the Global Cohort, with Final Analysis performed using a data cut-off of 27-Sep-2024.

End point type	Secondary
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End point timeframe:

Up to approximately 35 months (through sSAP pre-specified Final Analysis database cut-off date of 27-Sep-2024)

End point values	Lenvatinib+pe mbrolizumab	Standard of Care (SOC) treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	47		
Units: Participants	53	47		

Statistical analyses

No statistical analyses for this end point

Secondary: Global Cohort: Number of Participants Who Discontinue Study Treatment Due to an Adverse Event (AE)

End point title	Global Cohort: Number of Participants Who Discontinue Study Treatment Due to an Adverse Event (AE)
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End point description:

An adverse event is defined as any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention. The number of participants who discontinued any study treatment due to an adverse

event is presented. All randomized participants in the Global Cohort who received at least one dose of study treatment were analyzed. Two participants randomized to pembrolizumab plus lenvatinib group were incorrectly treated with SOC; these participants were included in the SOC group for safety analyses. Per the sSAP, Final Analysis for the Global Cohort was performed with a data cut-off date of 20-Feb-2023.

End point type	Secondary
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End point timeframe:

Up to approximately 22 months (through sSAP pre-specified Final Analysis database cut-off date of 20-Feb-2023)

End point values	Lenvatinib+pe mbrolizumab	Standard of Care (SOC) treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	238	235		
Units: Participants	37	10		

Statistical analyses

No statistical analyses for this end point

Secondary: China Cohort: Number of Participants Who Discontinue Study Treatment Due to an Adverse Event (AE)

End point title	China Cohort: Number of Participants Who Discontinue Study Treatment Due to an Adverse Event (AE)
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End point description:

An adverse event is defined as any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention. The number of participants who discontinued any study treatment due to an adverse event is reported. All randomized participants in the China Cohort who received at least one dose of study treatment were analyzed. Per the sSAP, the China Cohort was evaluated for safety separately from the Global Cohort, with Final Analysis performed using a data cut-off of 27-Sep-2024.

End point type	Secondary
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End point timeframe:

Up to approximately 28 months (through sSAP pre-specified Final Analysis database cut-off date of 27-Sep-2024)

End point values	Lenvatinib+pe mbrolizumab	Standard of Care (SOC) treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	47		
Units: Participants	8	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Global Cohort: Change from Baseline in European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) Global Health Status (Item 29) and Quality of Life (Item 30) Combined Score

End point title	Global Cohort: Change from Baseline in European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) Global Health Status (Item 29) and Quality of Life (Item 30) Combined Score
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End point description:

The EORTC QLQ-C30 is a cancer specific health-related quality-of life (QoL) questionnaire. Participant responses to the questions regarding Global Health Status (GHS; "How would you rate your overall health during the past week?") and Quality of Life (QoL; "How would you rate your overall quality of life during the past week?") are scored on a 7-point scale (1= Very poor to 7=Excellent). Using linear transformation, raw scores are standardized, so that scores range from 0 to 100. A higher score indicates a better outcome. The change from baseline in GHS (EORTC QLQ-C30 Item 29) and QoL (EORTC QLQ-C30 Item 30) combined score is presented for all participants in the Global Cohort who have at least one assessment available for EORTC QLQ-C30 and have received at least one dose of the study intervention. Per the sSAP, this Patient Reported Outcome (PRO) was not pre-specified for the China Cohort and was thus not analyzed.

End point type	Secondary
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End point timeframe:

Baseline and 8 weeks

End point values	Lenvatinib+pe mbrolizumab	Standard of Care (SOC) treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	234	229		
Units: Scores on a scale				
least squares mean (confidence interval 95%)	-4.91 (-7.67 to -2.14)	-7.62 (-10.48 to -4.76)		

Statistical analyses

Statistical analysis title	Difference in LS means at Week 8 (Items 29 & 30)
Comparison groups	Lenvatinib+pembrolizumab v Standard of Care (SOC) treatment
Number of subjects included in analysis	463
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1553 ^[5]
Method	cLDA model
Parameter estimate	Difference in least squares means
Point estimate	2.71

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.03
upper limit	6.46

Notes:

[5] - Based on a cLDA model with the PRO scores as the response variable with covariates for treatment by study visit interaction and stratification factor presence of liver metastasis (Yes/No).

Secondary: Global Cohort: Change from Baseline in EORTC QLQ-C30 Physical Functioning (Items 1-5) Score

End point title	Global Cohort: Change from Baseline in EORTC QLQ-C30 Physical Functioning (Items 1-5) Score
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End point description:

The EORTC QLQ-C30 is a cancer specific health-related quality-of life (QoL) questionnaire. Participant responses to 5 questions about their physical functioning (Items 1-5) are scored on a 4-point scale (1=Not at All to 4=Very Much). Using linear transformation, raw scores are standardized, so that scores range from 0 to 100. Higher scores meant a better level of function. The change from baseline in the EORTC QLQ-C30 Physical Functioning (Items 1-5) scale score is presented for all participants in the Global Cohort who have at least one assessment available for EORTC QLQ-C30 and have received at least one dose of the study intervention. Per the sSAP, this PRO was not pre-specified for the China Cohort and was thus not analyzed.

End point type	Secondary
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End point timeframe:

Baseline and 8 weeks

End point values	Lenvatinib+pembrolizumab	Standard of Care (SOC) treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	234	229		
Units: Scores on a scale				
least squares mean (confidence interval 95%)	-6.16 (-8.51 to -3.82)	-7.32 (-9.75 to -4.90)		

Statistical analyses

Statistical analysis title	Difference in LS means at Week 8 (Items 1-5)
Comparison groups	Lenvatinib+pembrolizumab v Standard of Care (SOC) treatment
Number of subjects included in analysis	463
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4967 ^[6]
Method	cLDA model
Parameter estimate	Difference in LS means
Point estimate	1.16

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.19
upper limit	4.51

Notes:

[6] - Based on a cLDA model with the PRO scores as the response variable with covariates for treatment by study visit interaction and stratification factor presence of liver metastasis (Yes/No).

Secondary: Global Cohort: Change from Baseline in EORTC QLQ-C30 Appetite Loss (Item 13) Score

End point title	Global Cohort: Change from Baseline in EORTC QLQ-C30 Appetite Loss (Item 13) Score
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End point description:

The EORTC QLQ-C30 is a cancer specific health-related quality-of life (QoL) questionnaire, including a single-item scale score for appetite loss (QLQ-C30 Item 13). For this item, individual responses to the question "Have you lacked appetite?" are given on a 4-point scale (1=Not at all; 4=Very much). Scores are transformed to a range from 0-100, with a lower score indicating a better outcome. The change from baseline in the EORTC QLQ-C30 appetite loss (Item 13) scale score is presented for all participants in the Global Cohort who have at least one assessment available for EORTC QLQ-C30 and have received at least one dose of the study intervention. Per the sSAP, this PRO was not pre-specified for the China Cohort and was thus not analyzed.

End point type	Secondary
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End point timeframe:

Baseline and 8 weeks

End point values	Lenvatinib+pembrolizumab	Standard of Care (SOC) treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	234	230		
Units: Scores on a scale				
least squares mean (confidence interval 95%)	12.44 (8.50 to 16.38)	9.08 (5.00 to 13.15)		

Statistical analyses

Statistical analysis title	Difference in LS means at Week 8 (Item 13)
Comparison groups	Lenvatinib+pembrolizumab v Standard of Care (SOC) treatment
Number of subjects included in analysis	464
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2271 ^[7]
Method	cLDA model
Parameter estimate	Difference in LS means
Point estimate	3.36

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	8.82

Notes:

[7] - Based on a cLDA model with the PRO scores as the response variable with covariates for treatment by study visit interaction and stratification factor presence of liver metastasis (Yes/No).

Secondary: Global Cohort: Change from Baseline in EORTC Quality of Life Questionnaire-Colorectal Cancer-Specific 29 Items (QLQ-CR29) Bloating (Item 37) Score

End point title	Global Cohort: Change from Baseline in EORTC Quality of Life Questionnaire-Colorectal Cancer-Specific 29 Items (QLQ-CR29) Bloating (Item 37) Score
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End point description:

The EORTC QLQ-CR29 is a health-related quality-of life (QoL) questionnaire specific for colorectal cancer, including a single-item scale score for bloating (QLQ-CR29 Item 37). For this item, individual responses to the question "Did you have a bloated feeling in your abdomen?" are given on a 4-point scale (1=Not at all; 4=Very much). Scores are transformed to a range from 0-100, with a lower score indicating a better outcome. The change from baseline in the EORTC QLQ-CR29 bloating (Item 37) scale score is presented for all participants in the Global Cohort who have at least one assessment available for EORTC QLQ-CR29 and have received at least one dose of the study intervention. Per the sSAP, this PRO was not pre-specified for the China Cohort and was thus not analyzed.

End point type	Secondary
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End point timeframe:

Baseline and 8 weeks

End point values	Lenvatinib+pe mbrolizumab	Standard of Care (SOC) treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	234	230		
Units: Scores on a scale				
least squares mean (confidence interval 95%)	-0.30 (-3.78 to 3.19)	5.16 (1.56 to 8.77)		

Statistical analyses

Statistical analysis title	Difference in LS means at Week 8 (Item 37)
Comparison groups	Lenvatinib+pembrolizumab v Standard of Care (SOC) treatment
Number of subjects included in analysis	464
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0264 ^[8]
Method	cLDA model
Parameter estimate	Difference in LS means
Point estimate	-5.46

Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.27
upper limit	-0.65

Notes:

[8] - Based on a cLDA model with the PRO scores as the response variable with covariates for treatment by study visit interaction and stratification factor presence of liver metastasis (Yes/No).

Secondary: Global Cohort: Time to Deterioration (TTD) in European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) Global Health Status (Item 29) and Quality of Life (Item 30) Combined Score

End point title	Global Cohort: Time to Deterioration (TTD) in European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) Global Health Status (Item 29) and Quality of Life (Item 30) Combined Score
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End point description:

TTD is defined as the time from baseline to the first onset of a ≥ 10 -point deterioration (decrease) from baseline in Global Health Status (GHS; EORTC QLQ-C30 Item 29) & Quality of Life (QoL; EORTC QLQ-C30 Item 30) combined score. Using linear transformation, raw scores are standardized, so that scores range from 0 to 100. A longer TTD indicates a better outcome. The TTD, as assessed based on a ≥ 10 -point negative change (decrease) from baseline in GHS and QoL combined score, is presented for all participants in the Global Cohort who have at least one assessment available for EORTC QLQ-C30 and have received at least one dose of the study intervention. Per the sSAP, this PRO was not pre-specified for the China Cohort and was thus not analyzed.

End point type	Secondary
End point timeframe:	
Up to approximately 21 months	

End point values	Lenvatinib+pe mbrolizumab	Standard of Care (SOC) treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	227	220		
Units: Months				
median (confidence interval 95%)	1.4 (1.1 to 1.9)	1.4 (1.0 to 1.8)		

Statistical analyses

Statistical analysis title	TTD (Item 29 & Item 30)
Comparison groups	Lenvatinib+pembrolizumab v Standard of Care (SOC) treatment
Number of subjects included in analysis	447
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4338 ^[9]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.91

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.14

Notes:

[9] - Two-sided p-value based on log-rank test stratified by presence of liver metastasis (Yes/No).

Secondary: Global Cohort: TTD in EORTC QLQ-C30 Physical Functioning (Items 1-5) Score

End point title	Global Cohort: TTD in EORTC QLQ-C30 Physical Functioning (Items 1-5) Score
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End point description:

TTD is defined as the time from baseline to the first onset of a ≥ 10 -point deterioration (decrease) from baseline in physical functioning score (QLQ-C30 Items 1-5). Using linear transformation, raw scores are standardized, so that scores range from 0 to 100. A longer TTD indicates a better outcome. The TTD, as assessed based on a ≥ 10 -point negative change (decrease) from baseline in physical functioning score, is presented for all participants in the Global Cohort who have at least one assessment available for EORTC QLQ-C30 and have received at least one dose of the study intervention. Per the sSAP, this PRO was not pre-specified for the China Cohort and was thus not analyzed.

End point type	Secondary
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End point timeframe:

Up to approximately 21 months

End point values	Lenvatinib+pembrolizumab	Standard of Care (SOC) treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	226	221		
Units: Months				
median (confidence interval 95%)	1.8 (1.4 to 2.0)	2.0 (1.4 to 2.3)		

Statistical analyses

Statistical analysis title	TTD (Items 1-5)
Comparison groups	Lenvatinib+pembrolizumab v Standard of Care (SOC) treatment
Number of subjects included in analysis	447
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4316 ^[10]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.38

Notes:

[10] - Two-sided p-value based on log-rank test stratified by presence of liver metastasis (Yes/No).

Secondary: Global Cohort: TTD in EORTC QLQ-C30 Appetite Loss (Item 13) Score

End point title	Global Cohort: TTD in EORTC QLQ-C30 Appetite Loss (Item 13) Score
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End point description:

TTD is defined as the time from baseline to the first onset of a ≥ 10 -point deterioration (increase) from baseline in appetite loss (QLQ-C30 Item 13) score. Using linear transformation, raw scores are standardized, so that scores range from 0 to 100. A longer TTD indicates a better outcome. The TTD, as assessed based on a ≥ 10 -point change (increase) from baseline in appetite loss score, is presented for all participants in the Global Cohort who have at least one assessment available for EORTC QLQ-C30 and have received at least one dose of the study intervention. Per the sSAP, this PRO was not pre-specified for the China Cohort and was thus not analyzed.

End point type	Secondary
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End point timeframe:

Up to approximately 21 months

End point values	Lenvatinib+pembrolizumab	Standard of Care (SOC) treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	226	221		
Units: Months				
median (confidence interval 95%)	1.4 (1.1 to 1.8)	1.4 (1.1 to 1.9)		

Statistical analyses

Statistical analysis title	TTD (Item 13)
Comparison groups	Lenvatinib+pembrolizumab v Standard of Care (SOC) treatment
Number of subjects included in analysis	447
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5587 ^[11]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	1.32

Notes:

[11] - Two-sided p-value based on log-rank test stratified by presence of liver metastasis (Yes/No).

Secondary: Global Cohort: TTD in EORTC Quality of Life Questionnaire-Colorectal Cancer-Specific 29 Items (QLQ-CR29) Bloating (Item 37) Score

End point title	Global Cohort: TTD in EORTC Quality of Life Questionnaire-Colorectal Cancer-Specific 29 Items (QLQ-CR29) Bloating (Item 37) Score
End point description:	
TTD is defined as the time from baseline to the first onset of a ≥ 10 -point deterioration (increase) from baseline in bloating (QLQ-CR29 Item 37) score. Using linear transformation, raw scores are standardized, so that scores range from 0 to 100. A longer TTD indicates a better outcome. The TTD, as assessed based on a ≥ 10 -point change (increase) from baseline in bloating score, is presented for all participants in the Global Cohort who have at least one assessment available for EORTC QLQ-CR29 and have received at least one dose of the study intervention. Per the sSAP, this PRO was not pre-specified for the China Cohort and was thus not analyzed.	
End point type	Secondary
End point timeframe:	
Up to approximately 21 months	

End point values	Lenvatinib+pe mbrolizumab	Standard of Care (SOC) treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224	221		
Units: Months				
median (confidence interval 95%)	3.4 (2.3 to 5.2)	3.2 (2.3 to 5.6)		

Statistical analyses

Statistical analysis title	TTD (Item 37)
Comparison groups	Lenvatinib+pembrolizumab v Standard of Care (SOC) treatment
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6794 ^[12]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.23

Notes:

[12] - Two-sided p-value based on log-rank test stratified by presence of liver metastasis (Yes/No).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 41 months (through End of Trial database cut-off date of 27-Sep-2024). 2 participants randomized to lenvatinib plus pembrolizumab were incorrectly treated with SOC and were included in SOC arm.

Adverse event reporting additional description:

All-cause deaths reported for all randomized participants (N=563). Serious and nonserious AEs include all treated participants according to treatment received. MedDRA V27.0 terms 'Neoplasm progression' 'Malignant neoplasm progression' and 'Disease progression' unrelated to the drug are excluded.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	27.0
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Reporting groups

Reporting group title	Standard Of Care Treatment
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Reporting group description:

Participants received regorafenib 160 mg via oral tablet once daily on Days 1 through 21 of each 4-week cycle OR TAS-102 (trifluridine and tipiracil hydrochloride) 35 mg/m² via oral tablet twice a day on Days 1 through 5 and Days 8-12 of each 4-week cycle until progressive disease.

Reporting group title	Lenvatinib + Pembrolizumab
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Reporting group description:

Participants received pembrolizumab 400 mg via intravenous (IV) infusion on Day 1 of each 6-week (Q6W) Cycle for up to 18 cycles (up to approximately 2 years) PLUS lenvatinib 20 mg via oral capsule once daily until progressive disease.

Serious adverse events	Standard Of Care Treatment	Lenvatinib + Pembrolizumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	66 / 277 (23.83%)	117 / 279 (41.94%)	
number of deaths (all causes)	264	251	
number of deaths resulting from adverse events	4	5	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Sinonasal papilloma			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			
subjects affected / exposed	2 / 277 (0.72%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			

Hypertension			
subjects affected / exposed	0 / 277 (0.00%)	6 / 279 (2.15%)	
occurrences causally related to treatment / all	0 / 0	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant hypertension			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Generalised oedema			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 277 (0.36%)	3 / 279 (1.08%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	1 / 277 (0.36%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

General physical health deterioration			
subjects affected / exposed	1 / 277 (0.36%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	4 / 277 (1.44%)	4 / 279 (1.43%)	
occurrences causally related to treatment / all	1 / 4	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Female genital tract fistula			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fluid collection			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			

subjects affected / exposed	1 / 277 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 277 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 277 (0.36%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	2 / 277 (0.72%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 277 (0.00%)	3 / 279 (1.08%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pneumothorax			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
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 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicide attempt			

subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device occlusion			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 277 (0.00%)	3 / 279 (1.08%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio increased			
subjects affected / exposed	1 / 277 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	1 / 277 (0.36%)	3 / 279 (1.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Granulocyte count decreased			
subjects affected / exposed	1 / 277 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium test positive			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

White blood cell count decreased subjects affected / exposed	1 / 277 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased subjects affected / exposed	1 / 277 (0.36%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Gastrointestinal anastomotic leak subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accidental overdose subjects affected / exposed	1 / 277 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stoma prolapse subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Wound complication			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
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 / 277 (0.36%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrioventricular block complete			
subjects affected / exposed	1 / 277 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 277 (0.00%)	2 / 279 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Coronary artery stenosis			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 277 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 277 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	1 / 277 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			

Brain stem infarction			
subjects affected / exposed	1 / 277 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amnesia			
subjects affected / exposed	1 / 277 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	1 / 277 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	0 / 277 (0.00%)	2 / 279 (0.72%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			

subjects affected / exposed	0 / 277 (0.00%)	2 / 279 (0.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embololic stroke			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cognitive disorder			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	0 / 277 (0.00%)	2 / 279 (0.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	2 / 277 (0.72%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	3 / 277 (1.08%)	2 / 279 (0.72%)	
occurrences causally related to treatment / all	2 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelosuppression			
subjects affected / exposed	2 / 277 (0.72%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	6 / 277 (2.17%)	5 / 279 (1.79%)	
occurrences causally related to treatment / all	1 / 6	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal inflammation			
subjects affected / exposed	1 / 277 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 277 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	3 / 277 (1.08%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	3 / 277 (1.08%)	4 / 279 (1.43%)	
occurrences causally related to treatment / all	4 / 4	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flatulence			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 277 (0.36%)	0 / 279 (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	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal perforation			

subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	3 / 277 (1.08%)	5 / 279 (1.79%)	
occurrences causally related to treatment / all	2 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-mediated enterocolitis			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-mediated pancreatitis			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal fistula			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 277 (0.36%)	4 / 279 (1.43%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	1 / 277 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal ulcer			

subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 277 (0.00%)	2 / 279 (0.72%)	
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 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 277 (0.36%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	2 / 277 (0.72%)	2 / 279 (0.72%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal ulcer			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal perforation			

subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	2 / 277 (0.72%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Proctitis			
subjects affected / exposed	1 / 277 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal perforation			
subjects affected / exposed	1 / 277 (0.36%)	0 / 279 (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	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 277 (0.72%)	2 / 279 (0.72%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 277 (0.00%)	3 / 279 (1.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			

subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis acute			
subjects affected / exposed	1 / 277 (0.36%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	3 / 277 (1.08%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary obstruction			
subjects affected / exposed	2 / 277 (0.72%)	2 / 279 (0.72%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	0 / 277 (0.00%)	2 / 279 (0.72%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	1 / 277 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder obstruction			
subjects affected / exposed	1 / 277 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			

subjects affected / exposed	1 / 277 (0.36%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertransaminasaemia			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic hepatitis			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant biliary obstruction			
subjects affected / exposed	1 / 277 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 277 (0.36%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 277 (0.36%)	4 / 279 (1.43%)	
occurrences causally related to treatment / all	0 / 1	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			

subjects affected / exposed	1 / 277 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-mediated nephritis			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proteinuria			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
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	1 / 277 (0.36%)	0 / 279 (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	1 / 277 (0.36%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric stenosis			
subjects affected / exposed	1 / 277 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
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			

Pathological fracture			
subjects affected / exposed	2 / 277 (0.72%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteolysis			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fistula			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in jaw			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal wall abscess			
subjects affected / exposed	1 / 277 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary sepsis			
subjects affected / exposed	1 / 277 (0.36%)	0 / 279 (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	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal sepsis			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	1 / 277 (0.36%)	4 / 279 (1.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			

subjects affected / exposed	1 / 277 (0.36%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fournier's gangrene			
subjects affected / exposed	1 / 277 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 277 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis E			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 277 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious pleural effusion			
subjects affected / exposed	1 / 277 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	1 / 277 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			
subjects affected / exposed	1 / 277 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			

subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 277 (1.08%)	5 / 279 (1.79%)	
occurrences causally related to treatment / all	2 / 3	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia bacterial			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
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 / 277 (0.72%)	3 / 279 (1.08%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Septic shock			
subjects affected / exposed	0 / 277 (0.00%)	2 / 279 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Skin infection			
subjects affected / exposed	1 / 277 (0.36%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelitis			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			

subjects affected / exposed	1 / 277 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spontaneous bacterial peritonitis			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	4 / 277 (1.44%)	6 / 279 (2.15%)	
occurrences causally related to treatment / all	0 / 5	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 277 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	2 / 277 (0.72%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			

subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 277 (0.00%)	2 / 279 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperammonaemia			
subjects affected / exposed	0 / 277 (0.00%)	1 / 279 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 277 (0.36%)	3 / 279 (1.08%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			
subjects affected / exposed	1 / 277 (0.36%)	0 / 279 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Standard Of Care Treatment	Lenvatinib + Pembrolizumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	263 / 277 (94.95%)	273 / 279 (97.85%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	63 / 277 (22.74%)	156 / 279 (55.91%)	
occurrences (all)	81	221	
General disorders and administration site conditions			
Malaise			
subjects affected / exposed	16 / 277 (5.78%)	14 / 279 (5.02%)	
occurrences (all)	18	15	
Fatigue			

subjects affected / exposed occurrences (all)	67 / 277 (24.19%) 81	78 / 279 (27.96%) 88	
Asthenia subjects affected / exposed occurrences (all)	36 / 277 (13.00%) 45	49 / 279 (17.56%) 62	
Mucosal inflammation subjects affected / exposed occurrences (all)	8 / 277 (2.89%) 8	18 / 279 (6.45%) 20	
Pyrexia subjects affected / exposed occurrences (all)	24 / 277 (8.66%) 32	40 / 279 (14.34%) 50	
Oedema peripheral subjects affected / exposed occurrences (all)	8 / 277 (2.89%) 8	26 / 279 (9.32%) 26	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	24 / 277 (8.66%) 27	29 / 279 (10.39%) 39	
Dysphonia subjects affected / exposed occurrences (all)	21 / 277 (7.58%) 24	57 / 279 (20.43%) 62	
Dyspnoea subjects affected / exposed occurrences (all)	21 / 277 (7.58%) 24	16 / 279 (5.73%) 18	
Epistaxis subjects affected / exposed occurrences (all)	2 / 277 (0.72%) 2	14 / 279 (5.02%) 16	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	20 / 277 (7.22%) 20	19 / 279 (6.81%) 21	
Investigations Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	17 / 277 (6.14%) 17	27 / 279 (9.68%) 33	
Aspartate aminotransferase increased			

subjects affected / exposed	39 / 277 (14.08%)	67 / 279 (24.01%)
occurrences (all)	49	90
Amylase increased		
subjects affected / exposed	5 / 277 (1.81%)	16 / 279 (5.73%)
occurrences (all)	7	17
Alanine aminotransferase increased		
subjects affected / exposed	30 / 277 (10.83%)	50 / 279 (17.92%)
occurrences (all)	38	68
Blood bilirubin increased		
subjects affected / exposed	41 / 277 (14.80%)	46 / 279 (16.49%)
occurrences (all)	52	60
Blood thyroid stimulating hormone increased		
subjects affected / exposed	2 / 277 (0.72%)	37 / 279 (13.26%)
occurrences (all)	2	57
Blood creatinine increased		
subjects affected / exposed	8 / 277 (2.89%)	21 / 279 (7.53%)
occurrences (all)	11	30
Gamma-glutamyltransferase increased		
subjects affected / exposed	9 / 277 (3.25%)	14 / 279 (5.02%)
occurrences (all)	9	15
Neutrophil count decreased		
subjects affected / exposed	48 / 277 (17.33%)	14 / 279 (5.02%)
occurrences (all)	151	34
Platelet count decreased		
subjects affected / exposed	32 / 277 (11.55%)	60 / 279 (21.51%)
occurrences (all)	59	91
Weight decreased		
subjects affected / exposed	26 / 277 (9.39%)	65 / 279 (23.30%)
occurrences (all)	27	69
White blood cell count decreased		
subjects affected / exposed	36 / 277 (13.00%)	15 / 279 (5.38%)
occurrences (all)	118	20
Nervous system disorders		

Dizziness subjects affected / exposed occurrences (all)	21 / 277 (7.58%) 24	19 / 279 (6.81%) 19	
Headache subjects affected / exposed occurrences (all)	14 / 277 (5.05%) 17	45 / 279 (16.13%) 61	
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	60 / 277 (21.66%) 73	49 / 279 (17.56%) 64	
Neutropenia subjects affected / exposed occurrences (all)	33 / 277 (11.91%) 82	8 / 279 (2.87%) 22	
Thrombocytopenia subjects affected / exposed occurrences (all)	12 / 277 (4.33%) 18	17 / 279 (6.09%) 25	
Gastrointestinal disorders			
Abdominal pain upper subjects affected / exposed occurrences (all)	16 / 277 (5.78%) 20	27 / 279 (9.68%) 29	
Abdominal pain subjects affected / exposed occurrences (all)	45 / 277 (16.25%) 56	58 / 279 (20.79%) 69	
Constipation subjects affected / exposed occurrences (all)	44 / 277 (15.88%) 58	43 / 279 (15.41%) 51	
Abdominal distension subjects affected / exposed occurrences (all)	14 / 277 (5.05%) 15	16 / 279 (5.73%) 21	
Diarrhoea subjects affected / exposed occurrences (all)	64 / 277 (23.10%) 85	119 / 279 (42.65%) 231	
Stomatitis subjects affected / exposed occurrences (all)	16 / 277 (5.78%) 18	30 / 279 (10.75%) 31	
Nausea			

subjects affected / exposed occurrences (all)	87 / 277 (31.41%) 139	66 / 279 (23.66%) 77	
Dry mouth subjects affected / exposed occurrences (all)	20 / 277 (7.22%) 21	24 / 279 (8.60%) 27	
Vomiting subjects affected / exposed occurrences (all)	49 / 277 (17.69%) 84	60 / 279 (21.51%) 83	
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	5 / 277 (1.81%) 6	20 / 279 (7.17%) 23	
Palmar-plantar erythrodysaesthesia syndrome subjects affected / exposed occurrences (all)	60 / 277 (21.66%) 74	59 / 279 (21.15%) 78	
Rash subjects affected / exposed occurrences (all)	17 / 277 (6.14%) 17	39 / 279 (13.98%) 44	
Renal and urinary disorders Proteinuria subjects affected / exposed occurrences (all)	42 / 277 (15.16%) 63	136 / 279 (48.75%) 200	
Endocrine disorders Hyperthyroidism subjects affected / exposed occurrences (all)	4 / 277 (1.44%) 5	14 / 279 (5.02%) 15	
Hypothyroidism subjects affected / exposed occurrences (all)	19 / 277 (6.86%) 23	105 / 279 (37.63%) 112	
Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all)	8 / 277 (2.89%) 8	29 / 279 (10.39%) 30	
Arthralgia subjects affected / exposed occurrences (all)	17 / 277 (6.14%) 19	50 / 279 (17.92%) 66	

Back pain subjects affected / exposed occurrences (all)	26 / 277 (9.39%) 29	34 / 279 (12.19%) 37	
Pain in extremity subjects affected / exposed occurrences (all)	10 / 277 (3.61%) 10	17 / 279 (6.09%) 22	
Infections and infestations			
Urinary tract infection subjects affected / exposed occurrences (all)	15 / 277 (5.42%) 17	28 / 279 (10.04%) 39	
COVID-19 subjects affected / exposed occurrences (all)	12 / 277 (4.33%) 12	27 / 279 (9.68%) 29	
Metabolism and nutrition disorders			
Hypoalbuminaemia subjects affected / exposed occurrences (all)	13 / 277 (4.69%) 18	34 / 279 (12.19%) 43	
Hypokalaemia subjects affected / exposed occurrences (all)	18 / 277 (6.50%) 25	20 / 279 (7.17%) 23	
Hyponatraemia subjects affected / exposed occurrences (all)	7 / 277 (2.53%) 7	19 / 279 (6.81%) 23	
Decreased appetite subjects affected / exposed occurrences (all)	69 / 277 (24.91%) 95	75 / 279 (26.88%) 90	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 March 2021	The primary change of Amendment 1 was to update per country Health Authorities and clarify information
26 May 2021	The primary change of Amendment 2 was to update lenvatinib toxicity information in response to a Health Authority request
29 August 2022	The primary change of Amendment 3 was to clarify metastatic liver subgroup language

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported