Clinical trial results:
A Phase 3 Randomized, Placebo-controlled Trial to Evaluate the Safety and Efficacy of Pembrolizumab (MK-3475) and Lenvatinib (E7080/MK-7902) Versus Pembrolizumab Alone as First-line Intervention in Participants with Advanced Melanoma (LEAP-003)

Summary

EudraCT number	2018-002520-16
Trial protocol	SE DE ES FR GB PL IT
Global end of trial date	01 November 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	MK-7902-003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03820986
WHO universal trial number (UTN)	-
Other trial identifiers	MSD: LEAP-003, Eisai Protocol Number: E7080-G000-312

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	01 November 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 January 2023
Global end of trial reached?	Yes
Global end of trial date	01 November 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 pembrolizumab (MK-3475) combined with lenvatinib (MK-7902/E7080) compared to pembrolizumab alone (with placebo for lenvatinib) as first-line treatment in adults with no prior systemic therapy for their advanced melanoma. The primary study hypotheses are that: 1) The combination of pembrolizumab and lenvatinib is superior to pembrolizumab and placebo as assessed by Progression-free Survival (PFS) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1), and 2) The combination of pembrolizumab and lenvatinib is superior to pembrolizumab and placebo as assessed by Overall Survival (OS). For this study, RECIST 1.1 has been modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

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	12 March 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 16
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Brazil: 35
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	Chile: 101
Country: Number of subjects enrolled	China: 62
Country: Number of subjects enrolled	France: 65
Country: Number of subjects enrolled	Germany: 32
Country: Number of subjects enrolled	Israel: 39
Country: Number of subjects enrolled	Italy: 78
Country: Number of subjects enrolled	Korea, Republic of: 35
Country: Number of subjects enrolled	Poland: 17
Country: Number of subjects enrolled	South Africa: 17
Country: Number of subjects enrolled	Spain: 113
Country: Number of subjects enrolled	Sweden: 16

Country: Number of subjects enrolled	Switzerland: 7
Country: Number of subjects enrolled	United Kingdom: 13
Country: Number of subjects enrolled	United States: 22
Worldwide total number of subjects	674
EEA total number of subjects	323

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)	367
From 65 to 84 years	294
85 years and over	13

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Adult participants with advanced melanoma, who have not received prior systemic therapy were enrolled. 674 participants were randomly assigned in a 1:1 ratio to either combination therapy, Pembrolizumab+Lenvatinib, or Pembrolizumab+Placebo, to assess the safety and efficacy of combination therapy, Pembrolizumab+Lenvatinib.

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	Subject, Investigator, Assessor, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Pembrolizumab+Lenvatinib

Arm description:

Participants received pembrolizumab 200 mg via intravenous (IV) infusion on Day 1 of each 3-week cycle for up to 35 administrations (up to approximately 2 years) PLUS lenvatinib 20 mg via oral capsule daily for up to at least 2 years.

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

Dosage and administration details:

20 mg via oral capsule daily for up to at least 2 years.

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

Dosage and administration details:

200 mg via intravenous (IV) infusion on Day 1 of each 3-week cycle for up to 35 administrations (up to approximately 2 years)

Arm title	Pembrolizumab+Placebo

Arm description:

Participants received pembrolizumab 200 mg via IV infusion on Day 1 of each 3-week cycle for up to 35 administrations (up to approximately 2 years) PLUS placebo for lenvatinib via oral capsule daily for up to at least 2 years.

Arm type	Active comparator

Investigational medicinal product name	Placebo for Lenvatinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo for Lenvatinib via oral capsule daily for up to at least 2 years.

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

Dosage and administration details:

200 mg via intravenous (IV) infusion on Day 1 of each 3-week cycle for up to 35 administrations (up to approximately 2 years)

Number of subjects in period 1	Pembrolizumab+Lenvatinib	Pembrolizumab+Placebo
Started	334	340
Treated	332	338
Completed	0	0
Not completed	334	340
Physician decision	1	-
Consent withdrawn by subject	9	4
Death	201	175
Sponsor Decision	122	160
Lost to follow-up	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Pembrolizumab+Lenvatinib
Reporting group description:	
Participants received pembrolizumab 200 mg via intravenous (IV) infusion on Day 1 of each 3-week cycle for up to 35 administrations (up to approximately 2 years) PLUS lenvatinib 20 mg via oral capsule daily for up to at least 2 years.	
Reporting group title	Pembrolizumab+Placebo
Reporting group description:	
Participants received pembrolizumab 200 mg via IV infusion on Day 1 of each 3-week cycle for up to 35 administrations (up to approximately 2 years) PLUS placebo for lenvatinib via oral capsule daily for up to at least 2 years.	

Reporting group values	Pembrolizumab+Lenvatinib	Pembrolizumab+Placebo	Total
Number of subjects	334	340	674
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)	180	187	367
From 65-84 years	145	149	294
85 years and over	9	4	13
Age Continuous Units: Years			
arithmetic mean	61.8	62.0	
standard deviation	± 14.0	± 13.1	-
Sex: Female, Male Units: Participants			
Female	125	139	264
Male	209	201	410
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	55	43	98
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	3	4
White	243	261	504
More than one race	1	2	3
Unknown or Not Reported	34	31	65
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	70	79	149
Not Hispanic or Latino	224	225	449

Unknown or Not Reported	40	36	76
Proto-oncogene B-Raf (BRAF) mutation positive			
Participants were stratified according to BRAF mutation status: BRAF mutation-positive, or BRAF wild-type or unknown.			
Units: Subjects			
No	211	215	426
Yes	123	125	248

End points

End points reporting groups

Reporting group title	Pembrolizumab+Lenvatinib
Reporting group description:	
Participants received pembrolizumab 200 mg via intravenous (IV) infusion on Day 1 of each 3-week cycle for up to 35 administrations (up to approximately 2 years) PLUS lenvatinib 20 mg via oral capsule daily for up to at least 2 years.	
Reporting group title	Pembrolizumab+Placebo
Reporting group description:	
Participants received pembrolizumab 200 mg via IV infusion on Day 1 of each 3-week cycle for up to 35 administrations (up to approximately 2 years) PLUS placebo for lenvatinib via oral capsule daily for up to at least 2 years.	

Primary: Progression-free Survival (PFS) as Assessed by Blinded Independent Central Review (BICR) per Modified Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)

End point title	Progression-free Survival (PFS) as Assessed by Blinded Independent Central Review (BICR) per Modified Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)
End point description:	
PFS is 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, PD is defined as ≥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 is also considered PD. For this study, RECIST 1.1 has been modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. The analysis population consisted of all randomized participants, included in the treatment group to which they were randomized. The final analysis for this end point is presented here.	
End point type	Primary
End point timeframe:	
Up to approximately 34 months	

End point values	Pembrolizumab +Lenvatinib	Pembrolizumab +Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	334	340		
Units: Months				
median (confidence interval 95%)	9.1 (6.4 to 11.8)	4.2 (3.1 to 6.3)		

Statistical analyses

Statistical analysis title	Pembrolizumab+Lenvatinib vs Pembrolizumab+Placebo
Comparison groups	Pembrolizumab+Lenvatinib v Pembrolizumab+Placebo

Number of subjects included in analysis	674
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.0176 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	0.98

Notes:

[1] - Based on Cox regression model with Efron's method of tie handling with treatment as a covariate and stratified by BRAF mutation positive (Yes vs. No). Hazard Ratio (HR)=Pembrolizumab + Lenvatinib vs. Pembrolizumab + Placebo

[2] - One-sided p-value based on log-rank test and stratified by BRAF mutation positive (Yes vs. No).

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS is defined as the time from date of randomization to date of death from any cause. The analysis population consisted of all randomized participants included in the treatment group to which they were randomized. The final analysis for this end point is presented here. A value of 9999 indicates that the upper limit was not reached.

End point type	Primary

End point timeframe:

Up to approximately 46 months

End point values	Pembrolizumab +Lenvatinib	Pembrolizumab +Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	334	340		
Units: Months				
median (confidence interval 95%)	25.8 (23.0 to 33.9)	39.5 (26.6 to 9999)		

Statistical analyses

Statistical analysis title	Pembrolizumab+Lenvatinib vs Pembrolizumab+Placebo
Comparison groups	Pembrolizumab+Lenvatinib v Pembrolizumab+Placebo
Number of subjects included in analysis	674
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.9521 [4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.97
upper limit	1.48

Notes:

[3] - HR based on Cox regression model with Efron’s method of tie handling with treatment as a covariate and stratified by BRAF mutation positive (Yes vs. No). HR=Pembrolizumab + Lenvatinib vs. Pembrolizumab + Placebo

[4] - One-sided p-value based on log-rank test and stratified by BRAF mutation positive (Yes vs. No).

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

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

End point description:

For participants who demonstrated CR (disappearance of all target lesions) or PR (at least a 30% decrease in sum of diameters of target lesions), DOR is defined as the date of the first documented evidence of CR or PR until disease progression or death from any cause, whichever occurs first. Per RECIST 1.1, PD is defined as ≥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. The appearance of one or more new lesions is also considered PD. RECIST 1.1 has been modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Analysis population is randomized participants with a confirmed complete or partial response included in the treatment group to which they were randomized. The final analysis for this end point is presented here. 9999 indicates value not reached at time of data cut-off due to insufficient number of participants with an event.

End point type	Secondary

End point timeframe:

Up to approximately 46 months

End point values	Pembrolizumab +Lenvatinib	Pembrolizumab +Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	145[5]	121[6]		
Units: Months				
median (full range (min-max))	26.9 (3.4 to 9999)	9999 (9999 to 9999)		

Notes:

[5] - Number of subjects analyzed is randomized participants with confirmed complete or partial response

[6] - Number of subjects analyzed is randomized participants with confirmed complete or partial response

Statistical analyses

No statistical analyses for this end point

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

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

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. For this study, RECIST 1.1 has been modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. The analysis population consisted of all randomized participants, included in the treatment group to which they were randomized. The final analysis for this end point is presented here.

End point type	Secondary

End point timeframe:

Up to approximately 46 months

End point values	Pembrolizumab +Lenvatinib	Pembrolizumab +Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	334	340		
Units: Percentage of participants				
number (confidence interval 95%)	43.4 (38.0 to 48.9)	35.6 (30.5 to 40.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Discontinue Study Treatment Due to Adverse Events (AEs)

End point title	Number of Participants Who Discontinue Study Treatment Due to Adverse Events (AEs)

End point description:

An AE is any untoward medical occurrence in a participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. The number of participants who discontinued any study treatment due to an AE is presented. The analysis population consisted of all randomized participants who received at least one dose of study intervention. The final analysis for this end point is presented here.

End point type	Secondary

End point timeframe:

Up to approximately 63 months

End point values	Pembrolizumab +Lenvatinib	Pembrolizumab +Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	332[7]	338[8]		
Units: Participants	104	68		

Notes:

[7] - Number of subjects analyzed is all randomized participants who got ≥1 dose of study treatment.

[8] - Number of subjects analyzed is all randomized participants who got ≥1 dose of study treatment.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events (AEs)

End point title	Number of Participants with Adverse Events (AEs)

End point description:

An AE is any untoward medical occurrence in a participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. The analysis population consisted of all randomized participants who received at least one dose of study intervention. The final analysis for this end point is presented here.

End point type	Secondary

End point timeframe:

Up to approximately 67 months

End point values	Pembrolizumab +Lenvatinib	Pembrolizumab +Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	332[9]	338[10]		
Units: Participants	331	330		

Notes:

[9] - Number of subjects analyzed is all randomized participants who got ≥1 dose of study treatment.

[10] - Number of subjects analyzed is all randomized participants who got ≥1 dose of study treatment.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in European Organization for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire-Core 30 [QLQ-C30] Global Health Status (GHS)/Quality of Life (QoL) Score

End point title	Change from Baseline in European Organization for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire-Core 30 [QLQ-C30] Global Health Status (GHS)/Quality of Life (QoL) Score

End point description:

The EORTC QLQ-C30 is a questionnaire to assess the overall quality of life of cancer patients. The GHS/QoL combined score consists of participant responses to the questions "How would you rate your overall health during the past week?" and "How would you rate your overall quality of life during the past week?" GHS/QoL responses range in score from 0 to 100, with a higher score indicating a better outcome. The analysis population consisted of all randomized participants who had at least 1 assessment available for the EORTC QLQ-C30 GHS/QoL score and had received at least 1 dose of study intervention. The final analysis for this end point is presented here.

End point type	Secondary

End point timeframe:

Baseline and Week 21

End point values	Pembrolizumab +Lenvatinib	Pembrolizumab +Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	325[11]	334[12]		
Units: Scores on a scale				
least squares mean (confidence interval 95%)	-6.38 (-8.91 to -3.84)	-2.69 (-5.30 to -0.08)		

Notes:

[11] - Subjects analyzed is randomized participants who got ≥1 dose of study drug & had ≥1 GHS/QoL Score
[12] - Subjects analyzed is randomized participants who got ≥1 dose of study drug & had ≥1 GHS/QoL Score

Statistical analyses

Statistical analysis title	Pembrolizumab+Lenvatinib vs Pembrolizumab+Placebo

Statistical analysis description:

Based on a constrained longitudinal data analysis (cLDA) model with GHS/QoL as the response variable, with covariates for treatment by time interaction, stratification factor BRAF mutation status as covariate. No formal hypothesis testing was conducted. P-value is nominal. Difference in Least Squared (LS) means= Pembrolizumab + Lenvatinib vs. Pembrolizumab + Placebo

Comparison groups	Pembrolizumab+Lenvatinib v Pembrolizumab+Placebo
Number of subjects included in analysis	659
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0345 [13]
Method	cLDA model
Parameter estimate	Difference in LS means
Point estimate	-3.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.1
upper limit	-0.27

Notes:

[13] - No formal hypothesis testing was conducted. P-value is nominal.

Secondary: Change from Baseline in European Organization for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire-Core 30 [QLQ-C30] Physical Function (PF) Score

End point title	Change from Baseline in European Organization for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire-Core 30 [QLQ-C30] Physical Function (PF) Score

End point description:

The EORTC QLQ-C30 is a questionnaire to assess the overall quality of life of cancer patients. The PF Score consists of participant responses to questions regarding PF (5 questions about daily activities [strenuous activities, long walks, short walks, bed/chair rest and needing help with eating, dressing, washing themselves or using the toilet]). For PF, responses range in score from 0 to 100, with a higher score indicating a better outcome. The analysis population consisted of all randomized participants who had at least 1 assessment available for the EORTC QLQ-C30 PF score and had received at least 1 dose of study intervention. The final analysis for this end point is presented here.

End point type	Secondary

End point timeframe:

Baseline and Week 21

End point values	Pembrolizumab +Lenvatinib	Pembrolizumab +Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	325[14]	334[15]		
Units: Scores on a scale				
least squares mean (confidence interval 95%)	-9.50 (-11.66 to -7.34)	-4.02 (-6.23 to -1.80)		

Notes:

[14] - Subjects analyzed is randomized participants who got ≥1 dose of study drug & had ≥1 PF Score

[15] - Subjects analyzed is randomized participants who got ≥1 dose of study drug & had ≥1 PF Score

Statistical analyses

Statistical analysis title	Pembrolizumab+Lenvatinib vs Pembrolizumab+Placebo

Statistical analysis description:

Based on a cLDA model with PF as the response variable, with covariates for treatment by time interaction, stratification factor BRAF mutation status as covariate. No formal hypothesis testing was conducted. P-value is nominal. Difference in Least Squared (LS) means= Pembrolizumab + Lenvatinib vs. Pembrolizumab + Placebo

Comparison groups	Pembrolizumab+Lenvatinib v Pembrolizumab+Placebo
Number of subjects included in analysis	659
Analysis specification	Pre-specified
Analysis type	other[16]
P-value	= 0.0004
Method	cLDA model
Parameter estimate	Difference in LS means
Point estimate	-5.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.53
upper limit	-2.45

Notes:

[16] - No formal hypothesis testing was conducted. P-value is nominal.

Secondary: Time to True Deterioration (TTD) Based on Change from Baseline in EORTC QLQ-C30 GHS/QoL score

End point title	Time to True Deterioration (TTD) Based on Change from Baseline in EORTC QLQ-C30 GHS/QoL score

End point description:

TTD is defined as the time from Baseline to 1st onset of a ≥10-point negative change (decrease) in EORTC-QLQ-C30 GHS Score. The EORTC QLQ-C30 is a questionnaire to assess the overall quality of life of cancer patients. The GHS/QoL Score consists of participant responses to the questions "How would you rate your overall health during the past week?" and "How would you rate your overall quality of life during the past week?" GHS/QoL responses range in score from 0 to 100, with a higher score indicating a better outcome. A longer TTD indicates a better outcome. The analysis population consisted of all randomized participants who have at least one assessment available for EORTC QLQ-C30 and have received at least one dose of the study intervention; and had data available for this TTD change from baseline in GHS/QoL outcome using EORTC QLQ-C30. The final analysis for this end point is presented here. 9999 indicates upper limit not reached.

End point type	Secondary

End point timeframe:

Up to approximately 30 months

End point values	Pembrolizumab +Lenvatinib	Pembrolizumab +Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	305[17]	323[18]		
Units: Months				
median (confidence interval 95%)	5.62 (4.34 to 9.69)	24.58 (11.04 to 9999)		

Notes:

[17] - Subjects analyzed is randomized participants who got ≥1 dose of study drug & had TTD GHS/QoL Score

[18] - Subjects analyzed is randomized participants who got ≥1 dose of study drug & had TTD GHS/QoL Score

Statistical analyses

Statistical analysis title	Pembrolizumab+Lenvatinib vs Pembrolizumab+Placebo

Statistical analysis description:

Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by BRAF mutation status (positive vs wild type or unknown). No formal hypothesis testing was conducted. P-value is nominal. HR=Lenvatinib + Pembrolizumab vs. Placebo + Pembrolizumab

Comparison groups	Pembrolizumab+Lenvatinib v Pembrolizumab+Placebo
Number of subjects included in analysis	628
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0001 [19]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.25
upper limit	2

Notes:

[19] - No formal hypothesis testing was conducted. P-value is nominal.

Secondary: Time to True Deterioration (TTD) Based on Change from Baseline in EORTC QLQ-C30 in Physical Function (PF) Score

End point title	Time to True Deterioration (TTD) Based on Change from Baseline in EORTC QLQ-C30 in Physical Function (PF) Score

End point description:

TTD is defined as the time from Baseline to 1st onset of a ≥10-point negative change (decrease) in EORTC-QLQ-C30 PF Score. The EORTC QLQ-C30 is a questionnaire to assess the overall quality of life of cancer patients. The PF Score consists of participant responses to questions regarding PF (5 questions about daily activities [strenuous activities, long walks, short walks, bed/chair rest & needing help with eating, dressing, washing themselves or using the toilet]. For PF, responses range in score from 0 to 100, with a higher score indicating a better outcome. The protocol-specified final analysis is presented. The analysis population consisted of all randomized participants who have at least one assessment available for EORTC QLQ-C30 and have received at least one dose of the study intervention; and had data available for this TTD change from baseline in PF Score outcome using EORTC QLQ-C30. The final analysis for this end point is presented here. 9999 indicates value not reached.

End point type	Secondary

End point timeframe:

Up to approximately 30 months

End point values	Pembrolizumab +Lenvatinib	Pembrolizumab +Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	305[20]	323[21]		
Units: Months				
median (confidence interval 95%)	5.55 (4.40 to 9.69)	9999 (9999 to 9999)		

Notes:

[20] - Subjects analyzed is randomized participants who got ≥1 dose of study drug & had TTD PF Score

[21] - Subjects analyzed is randomized participants who got ≥1 dose of study drug & had TTD PF Score

Statistical analyses

Statistical analysis title	Pembrolizumab+Lenvatinib vs Pembrolizumab+Placebo

Statistical analysis description:

Based on Cox regression model with Efron’s method of tie handling with treatment as a covariate stratified by BRAF mutation status (positive vs wild type or unknown). No formal hypothesis testing was conducted. P-value is nominal. HR=Lenvatinib + Pembrolizumab vs. Placebo + Pembrolizumab

Comparison groups	Pembrolizumab+Lenvatinib v Pembrolizumab+Placebo
Number of subjects included in analysis	628
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0001 [22]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.52
upper limit	2.5

Notes:

[22] - No formal hypothesis testing was conducted. P-value is nominal.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 67 months

Adverse event reporting additional description:

All Cause Mortality: all randomized participants included in the treatment group to which they were randomized. AEs: all randomized participants who got ≥1 dose of study intervention. Per protocol, MedDRA preferred terms "Neoplasm progression (NP), Malignant NP and Disease progression" not related to study drug are omitted as AEs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.1

Reporting groups

Reporting group title	Lenvatinib + Pembrolizumab
Reporting group description: -	
Reporting group title	Placebo + Pembrolizumab

Reporting group description: -

Serious adverse events	Lenvatinib + Pembrolizumab	Placebo + Pembrolizumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	124 / 332 (37.35%)	96 / 338 (28.40%)	
number of deaths (all causes)	206	176	
number of deaths resulting from adverse events	14	13	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	3 / 332 (0.90%)	2 / 338 (0.59%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer recurrent			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			

subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lentigo maligna			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma in situ			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm skin			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraneoplastic syndrome			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	2 / 332 (0.60%)	2 / 338 (0.59%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	1 / 332 (0.30%)	3 / 338 (0.89%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			

subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (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	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour ulceration			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma stage I			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesothelioma			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 332 (0.30%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	0 / 332 (0.00%)	2 / 338 (0.59%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	3 / 332 (0.90%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic shock			

subjects affected / exposed	2 / 332 (0.60%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Ectopic pregnancy			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 332 (0.30%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Fatigue			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 332 (0.00%)	2 / 338 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Non-cardiac chest pain			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyrexia			
subjects affected / exposed	4 / 332 (1.20%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	3 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Haemophagocytic lymphohistiocytosis			
subjects affected / exposed	1 / 332 (0.30%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 332 (0.30%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Immune-mediated lung disease			

subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Interstitial lung disease			
subjects affected / exposed	2 / 332 (0.60%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 332 (0.30%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 332 (0.30%)	3 / 338 (0.89%)	
occurrences causally related to treatment / all	1 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pneumothorax			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	5 / 332 (1.51%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	4 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary fibrosis			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			

subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	1 / 332 (0.30%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Amylase increased			
subjects affected / exposed	1 / 332 (0.30%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 332 (0.30%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical condition abnormal			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipase increased			

subjects affected / exposed	2 / 332 (0.60%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin T increased			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest injury			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	2 / 332 (0.60%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	2 / 332 (0.60%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			

subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic fracture			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access site inflammation			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shoulder fracture			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Tracheo-oesophageal fistula			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Acute coronary syndrome			
subjects affected / exposed	2 / 332 (0.60%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	4 / 332 (1.20%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	2 / 332 (0.60%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
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	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (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	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus bradycardia			

subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (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			
Dizziness			
subjects affected / exposed	1 / 332 (0.30%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amnesia			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	2 / 332 (0.60%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cognitive disorder			

subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis autoimmune			
subjects affected / exposed	1 / 332 (0.30%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Haemorrhagic stroke			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hemiparesis			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-mediated encephalitis			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myasthenic syndrome			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	2 / 332 (0.60%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	1 / 332 (0.30%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Guillain-Barre syndrome			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 332 (0.30%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Uveitis			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 332 (0.30%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pancreatitis			
subjects affected / exposed	4 / 332 (1.20%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune colitis			
subjects affected / exposed	1 / 332 (0.30%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic gastritis			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	3 / 332 (0.90%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	6 / 332 (1.81%)	4 / 338 (1.18%)	
occurrences causally related to treatment / all	6 / 7	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	1 / 332 (0.30%)	2 / 338 (0.59%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
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 / 332 (0.30%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-mediated enterocolitis			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	2 / 332 (0.60%)	2 / 338 (0.59%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic disorder			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic fistula			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	2 / 332 (0.60%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			

subjects affected / exposed	1 / 332 (0.30%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 332 (0.30%)	3 / 338 (0.89%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stone			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	3 / 332 (0.90%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			

subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertransaminasaemia			
subjects affected / exposed	0 / 332 (0.00%)	2 / 338 (0.59%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-mediated hepatitis			
subjects affected / exposed	3 / 332 (0.90%)	2 / 338 (0.59%)	
occurrences causally related to treatment / all	3 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal vein thrombosis			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis bullous			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug eruption			

subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic skin eruption			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephritis			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	4 / 332 (1.20%)	3 / 338 (0.89%)	
occurrences causally related to treatment / all	1 / 4	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune nephritis			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prerenal failure			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal injury			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			

subjects affected / exposed	1 / 332 (0.30%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Addison's disease			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adrenal insufficiency			
subjects affected / exposed	3 / 332 (0.90%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthyroidism			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocytic hypophysitis			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Axillary mass			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertrophic osteoarthropathy			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myositis			
subjects affected / exposed	1 / 332 (0.30%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Neck pain			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoporotic fracture			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Enteritis infectious			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal abscess			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal infection			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
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 / 332 (0.30%)	0 / 338 (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	2 / 332 (0.60%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (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 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	2 / 332 (0.60%)	5 / 338 (1.48%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
COVID-19 pneumonia			
subjects affected / exposed	3 / 332 (0.90%)	6 / 338 (1.78%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 2	0 / 3	
Cellulitis			
subjects affected / exposed	2 / 332 (0.60%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	3 / 332 (0.90%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			

subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	2 / 332 (0.60%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Rectal abscess			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma infection			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemophilus infection			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster oticus			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngeal candidiasis			

subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (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	1 / 332 (0.30%)	0 / 338 (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	5 / 332 (1.51%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	2 / 332 (0.60%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pneumococcal			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (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	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			

subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (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 / 332 (0.30%)	0 / 338 (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 bacterial			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 332 (0.30%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Septic shock			
subjects affected / exposed	2 / 332 (0.60%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Skin candida			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			

subjects affected / exposed	1 / 332 (0.30%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal bacteraemia			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tick-borne fever			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (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	1 / 332 (0.30%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	1 / 332 (0.30%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			

subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercholesterolaemia			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertriglyceridaemia			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitamin B1 deficiency			
subjects affected / exposed	0 / 332 (0.00%)	1 / 338 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 332 (0.30%)	0 / 338 (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	Lenvatinib + Pembrolizumab	Placebo + Pembrolizumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	326 / 332 (98.19%)	319 / 338 (94.38%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	203 / 332 (61.14%)	75 / 338 (22.19%)	
occurrences (all)	378	119	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	95 / 332 (28.61%)	82 / 338 (24.26%)	
occurrences (all)	164	122	
Fatigue			
subjects affected / exposed	92 / 332 (27.71%)	86 / 338 (25.44%)	
occurrences (all)	130	109	
Mucosal inflammation			
subjects affected / exposed	39 / 332 (11.75%)	10 / 338 (2.96%)	
occurrences (all)	54	12	
Oedema peripheral			
subjects affected / exposed	39 / 332 (11.75%)	34 / 338 (10.06%)	
occurrences (all)	43	43	
Pyrexia			
subjects affected / exposed	40 / 332 (12.05%)	42 / 338 (12.43%)	
occurrences (all)	50	60	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	43 / 332 (12.95%)	41 / 338 (12.13%)	
occurrences (all)	51	54	
Dysphonia			
subjects affected / exposed	54 / 332 (16.27%)	3 / 338 (0.89%)	
occurrences (all)	61	3	
Dyspnoea			
subjects affected / exposed	25 / 332 (7.53%)	25 / 338 (7.40%)	
occurrences (all)	30	27	
Epistaxis			
subjects affected / exposed	19 / 332 (5.72%)	3 / 338 (0.89%)	
occurrences (all)	20	3	

Oropharyngeal pain			
subjects affected / exposed	18 / 332 (5.42%)	4 / 338 (1.18%)	
occurrences (all)	22	4	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	25 / 332 (7.53%)	29 / 338 (8.58%)	
occurrences (all)	29	30	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	75 / 332 (22.59%)	55 / 338 (16.27%)	
occurrences (all)	118	89	
Amylase increased			
subjects affected / exposed	47 / 332 (14.16%)	37 / 338 (10.95%)	
occurrences (all)	73	72	
Aspartate aminotransferase increased			
subjects affected / exposed	82 / 332 (24.70%)	47 / 338 (13.91%)	
occurrences (all)	130	67	
Blood alkaline phosphatase increased			
subjects affected / exposed	34 / 332 (10.24%)	24 / 338 (7.10%)	
occurrences (all)	52	30	
Blood bilirubin increased			
subjects affected / exposed	40 / 332 (12.05%)	19 / 338 (5.62%)	
occurrences (all)	81	34	
Blood cholesterol increased			
subjects affected / exposed	36 / 332 (10.84%)	13 / 338 (3.85%)	
occurrences (all)	77	27	
Blood creatine phosphokinase increased			
subjects affected / exposed	49 / 332 (14.76%)	41 / 338 (12.13%)	
occurrences (all)	77	73	
Blood creatinine increased			
subjects affected / exposed	42 / 332 (12.65%)	26 / 338 (7.69%)	
occurrences (all)	73	48	
Blood glucose increased			
subjects affected / exposed	18 / 332 (5.42%)	16 / 338 (4.73%)	
occurrences (all)	40	28	
Blood lactate dehydrogenase			

increased			
subjects affected / exposed	33 / 332 (9.94%)	21 / 338 (6.21%)	
occurrences (all)	63	28	
Blood sodium decreased			
subjects affected / exposed	21 / 332 (6.33%)	10 / 338 (2.96%)	
occurrences (all)	46	19	
Blood thyroid stimulating hormone increased			
subjects affected / exposed	56 / 332 (16.87%)	18 / 338 (5.33%)	
occurrences (all)	79	36	
Blood triglycerides increased			
subjects affected / exposed	31 / 332 (9.34%)	22 / 338 (6.51%)	
occurrences (all)	67	43	
Blood urea increased			
subjects affected / exposed	21 / 332 (6.33%)	14 / 338 (4.14%)	
occurrences (all)	38	43	
Gamma-glutamyltransferase increased			
subjects affected / exposed	36 / 332 (10.84%)	23 / 338 (6.80%)	
occurrences (all)	49	30	
Lipase increased			
subjects affected / exposed	85 / 332 (25.60%)	61 / 338 (18.05%)	
occurrences (all)	171	115	
Platelet count decreased			
subjects affected / exposed	26 / 332 (7.83%)	3 / 338 (0.89%)	
occurrences (all)	42	3	
Weight decreased			
subjects affected / exposed	91 / 332 (27.41%)	30 / 338 (8.88%)	
occurrences (all)	111	36	
Nervous system disorders			
Dizziness			
subjects affected / exposed	40 / 332 (12.05%)	27 / 338 (7.99%)	
occurrences (all)	54	29	
Dysgeusia			
subjects affected / exposed	23 / 332 (6.93%)	5 / 338 (1.48%)	
occurrences (all)	32	6	
Headache			

subjects affected / exposed	76 / 332 (22.89%)	51 / 338 (15.09%)	
occurrences (all)	131	59	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	40 / 332 (12.05%)	53 / 338 (15.68%)	
occurrences (all)	58	70	
Thrombocytopenia			
subjects affected / exposed	21 / 332 (6.33%)	6 / 338 (1.78%)	
occurrences (all)	32	6	
Neutropenia			
subjects affected / exposed	25 / 332 (7.53%)	8 / 338 (2.37%)	
occurrences (all)	43	16	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	58 / 332 (17.47%)	40 / 338 (11.83%)	
occurrences (all)	96	45	
Abdominal pain upper			
subjects affected / exposed	47 / 332 (14.16%)	19 / 338 (5.62%)	
occurrences (all)	58	22	
Constipation			
subjects affected / exposed	59 / 332 (17.77%)	50 / 338 (14.79%)	
occurrences (all)	90	60	
Diarrhoea			
subjects affected / exposed	171 / 332 (51.51%)	84 / 338 (24.85%)	
occurrences (all)	454	141	
Dry mouth			
subjects affected / exposed	36 / 332 (10.84%)	23 / 338 (6.80%)	
occurrences (all)	39	26	
Dyspepsia			
subjects affected / exposed	31 / 332 (9.34%)	12 / 338 (3.55%)	
occurrences (all)	39	13	
Nausea			
subjects affected / exposed	111 / 332 (33.43%)	61 / 338 (18.05%)	
occurrences (all)	204	85	
Stomatitis			

subjects affected / exposed	30 / 332 (9.04%)	4 / 338 (1.18%)	
occurrences (all)	43	4	
Vomiting			
subjects affected / exposed	75 / 332 (22.59%)	38 / 338 (11.24%)	
occurrences (all)	134	51	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	21 / 332 (6.33%)	12 / 338 (3.55%)	
occurrences (all)	23	12	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	52 / 332 (15.66%)	4 / 338 (1.18%)	
occurrences (all)	71	4	
Pruritus			
subjects affected / exposed	68 / 332 (20.48%)	78 / 338 (23.08%)	
occurrences (all)	81	114	
Rash			
subjects affected / exposed	62 / 332 (18.67%)	57 / 338 (16.86%)	
occurrences (all)	89	75	
Vitiligo			
subjects affected / exposed	21 / 332 (6.33%)	41 / 338 (12.13%)	
occurrences (all)	23	41	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	100 / 332 (30.12%)	35 / 338 (10.36%)	
occurrences (all)	177	61	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	44 / 332 (13.25%)	17 / 338 (5.03%)	
occurrences (all)	48	18	
Hypothyroidism			
subjects affected / exposed	157 / 332 (47.29%)	44 / 338 (13.02%)	
occurrences (all)	198	50	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	100 / 332 (30.12%)	69 / 338 (20.41%)	
occurrences (all)	162	100	

Back pain			
subjects affected / exposed	64 / 332 (19.28%)	42 / 338 (12.43%)	
occurrences (all)	78	56	
Myalgia			
subjects affected / exposed	63 / 332 (18.98%)	42 / 338 (12.43%)	
occurrences (all)	76	52	
Pain in extremity			
subjects affected / exposed	31 / 332 (9.34%)	32 / 338 (9.47%)	
occurrences (all)	37	38	
Infections and infestations			
COVID-19			
subjects affected / exposed	21 / 332 (6.33%)	28 / 338 (8.28%)	
occurrences (all)	21	33	
Urinary tract infection			
subjects affected / exposed	28 / 332 (8.43%)	35 / 338 (10.36%)	
occurrences (all)	39	44	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	113 / 332 (34.04%)	54 / 338 (15.98%)	
occurrences (all)	166	58	
Hypercholesterolaemia			
subjects affected / exposed	35 / 332 (10.54%)	18 / 338 (5.33%)	
occurrences (all)	64	27	
Hyperglycaemia			
subjects affected / exposed	52 / 332 (15.66%)	39 / 338 (11.54%)	
occurrences (all)	92	62	
Hypertriglyceridaemia			
subjects affected / exposed	59 / 332 (17.77%)	28 / 338 (8.28%)	
occurrences (all)	118	49	
Hyperuricaemia			
subjects affected / exposed	17 / 332 (5.12%)	9 / 338 (2.66%)	
occurrences (all)	29	16	
Hypoalbuminaemia			
subjects affected / exposed	21 / 332 (6.33%)	8 / 338 (2.37%)	
occurrences (all)	33	9	
Hypokalaemia			

subjects affected / exposed	37 / 332 (11.14%)	16 / 338 (4.73%)	
occurrences (all)	51	23	
Hyponatraemia			
subjects affected / exposed	37 / 332 (11.14%)	20 / 338 (5.92%)	
occurrences (all)	57	26	
Hypomagnesaemia			
subjects affected / exposed	20 / 332 (6.02%)	9 / 338 (2.66%)	
occurrences (all)	27	13	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 March 2019	Amendment 01: To address feedback from regulatory authority and add MK-7902 program level updates.
24 April 2020	Amendment 02: To clarify AE safety follow-up timelines, to clarify allowed concomitant medications, and to add MK-7902 program level updates.
01 July 2021	Amendment 03: To update the Dose Modification and Toxicity Management Guidelines for irAEs and table for alignment with the USPI as requested by the FDA.
16 September 2021	Amendment 04: Due to slower than expected Overall Survival event rate, a third IA for Overall Survival was added. IA strategies were adjusted to achieve optimal timing for IAs.
03 October 2022	Amendment 06: Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
31 July 2023	Amendment 07: Protocol amended consistent with recommendations of the eDMC after an interim review of the data; specifically, to discontinue the study due to lack of efficacy.
11 December 2023	Amendment 08: This change was made to address incorrect standard text that was inadvertently changed in Amendment 07. The language was reverted to text provided in Amendment 06 to maintain consistency within the study.
07 April 2024	Amendment 09: The changes in this amendment are related to study extension. The changes allow additional data collection and longer follow-up for all participants enrolled in China.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported