Clinical trial results:
A Phase 3, Randomized, Double-blind Study to Compare the Efficacy and Safety of Pembrolizumab (MK-3475) in Combination with Lenvatinib (E7080/MK-7902) Versus Pembrolizumab and Placebo as First Line Treatment for Locally Advanced or Metastatic Urothelial Carcinoma in Cisplatin-ineligible Participants Whose Tumors Express PD-L1, and in Participants Ineligible for Any Platinum-containing Chemotherapy Regardless of PD-L1 Expression (LEAP-011)

Summary

EudraCT number	2018-003752-21
Trial protocol	FR HU PL NL DK ES GB IT
Global end of trial date	20 May 2024

Results information

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

Trial information

Trial identification

Sponsor protocol code	MK-7902-011

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03898180
WHO universal trial number (UTN)	-
Other trial identifiers	JAPIC-CTI: 194808, Eisai: E7080-G000-317, LEAP-011: MSD

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme LLC
Sponsor organisation address	126 East Lincoln Avenue, P.O. Box 2000, Rahway, 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	26 July 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 July 2021
Global end of trial reached?	Yes
Global end of trial date	20 May 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to evaluate the efficacy and safety of lenvatinib (MK-7902/E7080) in combination with pembrolizumab (MK-3475) in participants with advanced/unresectable or metastatic urothelial carcinoma.
The primary hypotheses were: 1. Pembrolizumab + lenvatinib is superior to pembrolizumab + placebo with respect to progression-free survival per Response Evaluation Criteria in Solid Tumors Version 1.1 by blinded independent central review, and 2. Pembrolizumab + lenvatinib is superior to pembrolizumab + placebo with respect to overall survival.
Based on recommendation of the external Data Monitoring Committee (eDMC), Amendment 3 (effective: 24-Sep-2021) unblinded the study and discontinued lenvatinib and placebo treatment. The eDMC was disbanded. With Amendment 4 (effective: 05-Dec-2022) second course pembrolizumab was no longer offered. Any participant receiving second course pembrolizumab treatment prior to Amendment 4 was able to complete treatment as planned.

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	06 May 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	Argentina: 31
Country: Number of subjects enrolled	Australia: 9
Country: Number of subjects enrolled	Canada: 19
Country: Number of subjects enrolled	China: 34
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Denmark: 6
Country: Number of subjects enrolled	Spain: 17
Country: Number of subjects enrolled	France: 33
Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	Hungary: 37

Country: Number of subjects enrolled	Israel: 13
Country: Number of subjects enrolled	Italy: 27
Country: Number of subjects enrolled	Japan: 34
Country: Number of subjects enrolled	Korea, Republic of: 58
Country: Number of subjects enrolled	Netherlands: 11
Country: Number of subjects enrolled	Poland: 43
Country: Number of subjects enrolled	Russian Federation: 41
Country: Number of subjects enrolled	Türkiye: 40
Country: Number of subjects enrolled	Taiwan: 30
Country: Number of subjects enrolled	United States: 8
Worldwide total number of subjects	505
EEA total number of subjects	181

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)	97
From 65 to 84 years	386
85 years and over	22

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Per protocol, response/progression or adverse events (AEs) that occurred during the second course of pembrolizumab were not included in efficacy or safety outcome measures.

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

Blinding implementation details:

The study was unblinded with Amendment 3.

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 21-day cycle for up to 35 cycles (up to approximately 2 years) PLUS lenvatinib 20 mg via oral capsule once daily (QD) until progressive disease (PD) or discontinuation. With protocol amendment 3 (effective: 24-Sep-2021), participants discontinued lenvatinib.

At the investigator’s discretion, eligible participants randomized to the pembrolizumab PLUS lenvatinib arm who completed the first course of pembrolizumab or who had stopped pembrolizumab due to confirmed complete response (CR) initiated a second course of pembrolizumab (200 mg IV infusion on Day 1 of each 21-day cycle, for up to 17 cycles [up to approximately 1 additional year]) upon experiencing PD.

Arm type	Experimental
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:

200 mg IV infusion, administered on Day 1 of each 21-day cycle for up to 35 cycles (up to approximately 2 years)

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

Dosage and administration details:

20 mg via oral capsule, administered QD until PD or discontinuation

Arm title	Pembrolizumab + Placebo

Arm description:

Participants received pembrolizumab 200 mg via IV infusion on Day 1 of each 21-day cycle for up to 35 cycles (up to approximately 2 years) PLUS placebo for lenvatinib via oral capsule QD until PD or discontinuation. With protocol amendment 3 (effective: 24-Sep-2021), participants discontinued placebo.

At the investigator’s discretion, eligible participants randomized to the pembrolizumab PLUS placebo arm who completed the first course of pembrolizumab, or who had stopped pembrolizumab due to confirmed CR, initiated a second course of pembrolizumab (200 mg IV infusion on Day 1 of each 21-day cycle, for up to 17 cycles [up to approximately 1 additional year]) upon experiencing PD.

Arm type	Experimental
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:

200 mg IV infusion, administered on Day 1 of each 21-day cycle for up to 35 cycles (up to approximately 2 years)

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 as an oral capsule, administered QD until PD or discontinuation

Number of subjects in period 1	Pembrolizumab + Lenvatinib	Pembrolizumab + Placebo
Started	251	254
Treated	247	254
Efficacy Analyses	245	242
Safety Analyses	241	242
Received Second Course of Pembrolizumab	2 [1]	5 [2]
Completed	63	77
Not completed	188	177
Physician decision	1	-
Consent withdrawn by subject	5	4
Death	178	173
Sponsor Decision	3	-
Lost to follow-up	1	-

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: At the investigator’s discretion, eligible participants randomized to the pembrolizumab PLUS placebo arm who completed the first course of pembrolizumab, or who had stopped pembrolizumab due to confirmed CR, initiated a second course of pembrolizumab (200 mg IV infusion on Day 1 of each 21-day cycle, for up to 17 cycles [up to approximately 1 additional year]) upon experiencing PD.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: At the investigator’s discretion, eligible participants randomized to the pembrolizumab PLUS placebo arm who completed the first course of pembrolizumab, or who had stopped

pembrolizumab due to confirmed CR, initiated a second course of pembrolizumab (200 mg IV infusion on Day 1 of each 21-day cycle, for up to 17 cycles [up to approximately 1 additional year]) upon experiencing PD.

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 21-day cycle for up to 35 cycles (up to approximately 2 years) PLUS lenvatinib 20 mg via oral capsule once daily (QD) until progressive disease (PD) or discontinuation. With protocol amendment 3 (effective: 24-Sep-2021), participants discontinued lenvatinib.

At the investigator's discretion, eligible participants randomized to the pembrolizumab PLUS lenvatinib arm who completed the first course of pembrolizumab or who had stopped pembrolizumab due to confirmed complete response (CR) initiated a second course of pembrolizumab (200 mg IV infusion on Day 1 of each 21-day cycle, for up to 17 cycles [up to approximately 1 additional year]) upon experiencing PD.

Reporting group title	Pembrolizumab + Placebo

Reporting group description:

Participants received pembrolizumab 200 mg via IV infusion on Day 1 of each 21-day cycle for up to 35 cycles (up to approximately 2 years) PLUS placebo for lenvatinib via oral capsule QD until PD or discontinuation. With protocol amendment 3 (effective: 24-Sep-2021), participants discontinued placebo.

At the investigator's discretion, eligible participants randomized to the pembrolizumab PLUS placebo arm who completed the first course of pembrolizumab, or who had stopped pembrolizumab due to confirmed CR, initiated a second course of pembrolizumab (200 mg IV infusion on Day 1 of each 21-day cycle, for up to 17 cycles [up to approximately 1 additional year]) upon experiencing PD.

Reporting group values	Pembrolizumab + Lenvatinib	Pembrolizumab + Placebo	Total
Number of subjects	251	254	505
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)	48	49	97
From 65-84 years	191	195	386
85 years and over	12	10	22
Age Continuous Units: Years			
arithmetic mean	72.3	71.9	
standard deviation	± 9.3	± 8.5	-
Sex: Female, Male Units: Participants			
Female	77	59	136
Male	174	195	369
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	78	79	157

Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	164	157	321
More than one race	0	1	1
Unknown or Not Reported	9	16	25
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	17	10	27
Not Hispanic or Latino	213	218	431
Unknown or Not Reported	21	26	47
Chemotherapy Ineligibility, Combined Positive Score (CPS), Eastern Cooperative Oncology Group (ECOG)			
Participants were classified as ineligible for any platinum agent or for cisplatin. CPS=PD-L1 immunohistochemistry positive cell (tumor cell, macrophage, lymphocyte) number divided by total tumor cells expressed as a percentage; classified as CPS ≥10 or <10. ECOG 0=fully active, ECOG 1=strenuous activity restricted, ECOG 2=in bed <50% of time; classified as ECOG=2 or 0/1. Per protocol stratification: (1) Ineligible for any platinum agents CPS ≥10 ECOG 2; (2) Ineligible for any platinum agents CPS <10 ECOG 2; (3) Cisplatin-ineligible CPS ≥10 ECOG 2; (4) Cisplatin-ineligible CPS ≥10 ECOG 0 or 1.			
Units: Subjects			
Ineligible for any platinum agents CPS ≥10 ECOG 2	83	84	167
Ineligible for any platinum agents CPS <10 ECOG 2	118	120	238
Cisplatin-ineligible CPS ≥10 ECOG 2	8	8	16
Cisplatin-ineligible CPS ≥10 ECOG 0 or 1	42	42	84

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 21-day cycle for up to 35 cycles (up to approximately 2 years) PLUS lenvatinib 20 mg via oral capsule once daily (QD) until progressive disease (PD) or discontinuation. With protocol amendment 3 (effective: 24-Sep-2021), participants discontinued lenvatinib.

At the investigator's discretion, eligible participants randomized to the pembrolizumab PLUS lenvatinib arm who completed the first course of pembrolizumab or who had stopped pembrolizumab due to confirmed complete response (CR) initiated a second course of pembrolizumab (200 mg IV infusion on Day 1 of each 21-day cycle, for up to 17 cycles [up to approximately 1 additional year]) upon experiencing PD.

Reporting group title	Pembrolizumab + Placebo

Reporting group description:

Participants received pembrolizumab 200 mg via IV infusion on Day 1 of each 21-day cycle for up to 35 cycles (up to approximately 2 years) PLUS placebo for lenvatinib via oral capsule QD until PD or discontinuation. With protocol amendment 3 (effective: 24-Sep-2021), participants discontinued placebo.

At the investigator's discretion, eligible participants randomized to the pembrolizumab PLUS placebo arm who completed the first course of pembrolizumab, or who had stopped pembrolizumab due to confirmed CR, initiated a second course of pembrolizumab (200 mg IV infusion on Day 1 of each 21-day cycle, for up to 17 cycles [up to approximately 1 additional year]) upon experiencing PD.

Primary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)

End point description:

PFS was defined as the time from randomization to the first documented PD per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) by blinded independent central review (BICR), or death due to any cause, whichever occurs first. Per RECIST 1.1, PD was defined as ≥20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also have demonstrated an absolute increase of ≥5 mm. The appearance of one or more new lesions was also considered PD. PFS as assessed by BICR per RECIST 1.1 is presented. Protocol-specified final analysis for this primary outcome measure was performed with an analysis data cut-off date of 26-Jul-2021. All participants randomized prior to the protocol-specified primary completion analysis data cut-off were analyzed.

End point type	Primary

End point timeframe:

Up to approximately 25 months

End point values	Pembrolizumab + Lenvatinib	Pembrolizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	245	242		
Units: Months				
median (confidence interval 95%)	4.5 (4.0 to 6.0)	4.0 (2.7 to 5.4)		

Statistical analyses

Statistical analysis title	PFS in Participants Randomized Before Data Cut-off

Statistical analysis description:

PFS of participants in the pembrolizumab + lenvatinib arm was compared to PFS of participants in the pembrolizumab + placebo arm based on the Cox regression model with Efron's method of tie handling with treatment as a covariate stratified on chemotherapy ineligibility, PD-L1 CPS, and ECOG PS.

Comparison groups	Pembrolizumab + Lenvatinib v Pembrolizumab + Placebo
Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4107 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.14

Notes:

[1] - Two-sided p-value based on log rank test stratified on chemotherapy ineligibility, programmed cell death ligand 1 (PD-L1) CPS, and ECOG performance status (PS).

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from randomization to death due to any cause. Participants without documented death at the time of the final analysis were to be censored at the date of the last follow-up. Protocol-specified final analysis for this primary outcome measure was performed with an analysis data cut-off date of 26-Jul-2021. All participants randomized prior to the protocol-specified primary completion analysis data cut-off were analyzed.

End point type	Primary

End point timeframe:

Up to approximately 25 months

End point values	Pembrolizumab + Lenvatinib	Pembrolizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	245	242		
Units: Months				
median (confidence interval 95%)	11.8 (9.1 to 15.1)	12.9 (9.8 to 17.8)		

Statistical analyses

Statistical analysis title	OS in Participants Randomized Before Data Cut-off

Statistical analysis description:

OS of participants in the pembrolizumab + lenvatinib arm was compared to OS of participants in the pembrolizumab + placebo arm based on the Cox regression model with Efron's method of tie handling

with treatment as a covariate stratified on chemotherapy ineligibility, PDL1 CPS, and ECOG PS.

Comparison groups	Pembrolizumab + Lenvatinib v Pembrolizumab + Placebo
Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3505 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.48

Notes:

[2] - Two-sided p-value based on log rank test stratified on chemotherapy ineligibility, PD-L1 CPS, and ECOG PS.

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

ORR was defined as the percentage of participants who had a confirmed CR (CR: disappearance of all target lesions) or partial response (PR: at least a 30% decrease in the sum of diameters of target lesions) per RECIST 1.1 as assessed by BICR. The percentage of participants who experienced a CR or PR is presented. Protocol-specified final analysis for this secondary outcome measure was performed with an analysis data cut-off date of 26-Jul-2021. All participants randomized prior to the protocol-specified primary completion analysis data cut-off were analyzed.

End point type	Secondary

End point timeframe:

Up to approximately 25 months

End point values	Pembrolizumab + Lenvatinib	Pembrolizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	245	242		
Units: Percentage of Participants				
number (confidence interval 95%)	33.1 (27.2 to 39.3)	28.9 (23.3 to 35.1)		

Statistical analyses

Statistical analysis title	ORR in Participants Randomized Before Data Cut-off

Statistical analysis description:

ORR of participants in the pembrolizumab + lenvatinib arm was compared to ORR of participants in the pembrolizumab + placebo arm based on the Miettinen & Nurminen method stratified on chemotherapy ineligibility, PD-L1 CPS, and ECOG PS.

Comparison groups	Pembrolizumab + Lenvatinib v Pembrolizumab + Placebo

Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in Percentage
Point estimate	4.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4
upper limit	12.2

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

For participants with confirmed CR (CR: disappearance of all target lesions) or partial response (PR: ≥30% decrease in the sum of diameters of target lesions) per BICR-assessed RECIST 1.1, DOR = time from first documented CR or PR until PD or death. PD was defined as ≥20% increase in the sum of diameters of target lesions and an absolute increase of ≥5 mm in the sum of diameters. The appearance of ≥1 new lesion was also considered PD. The DOR for participants who experienced a confirmed CR or PR is presented. Protocol-specified final analysis for this secondary outcome measure was performed with an analysis data cut-off date of 26-Jul-2021. All participants randomized prior to the protocol-specified primary completion analysis data cut-off and who also experienced a confirmed complete response or partial response were analyzed. 9999=Median, upper limit, and lower limit could not be reached at time of data cut-off due to insufficient number of responding participants with relapse.

End point type	Secondary

End point timeframe:

Up to approximately 25 months

End point values	Pembrolizumab + Lenvatinib	Pembrolizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	70		
Units: Months				
median (full range (min-max))	9999 (9999 to 9999)	9999 (9999 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR)

End point title	Disease Control Rate (DCR)

End point description:

DCR was defined as the percentage of participants who have a CR (CR: disappearance of all target lesions) or partial response (PR: at least a 30% decrease in the sum of diameters of target lesions) or stable disease (SD: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD [PD: ≥20% increase in the sum of diameters of target lesions and an absolute increase of ≥5 mm. The appearance of one or more new lesions was also considered PD]). DCR for participants who had not

progressed or died at the time of analysis was to be censored at the date of their last tumor assessment. The DCR as assessed by BICR per RECIST 1.1 is presented. Protocol-specified final analysis for this secondary outcome measure was performed with an analysis data cut-off date of 26-Jul-2021. All participants randomized prior to the protocol-specified primary completion analysis data cut-off were analyzed.

End point type	Secondary

End point timeframe:

Up to approximately 25 months

End point values	Pembrolizumab + Lenvatinib	Pembrolizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	245	242		
Units: Percentage of Participants				
number (confidence interval 95%)	66.9 (60.7 to 72.8)	56.2 (49.7 to 62.5)		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

The EORTC QLQ-C30 is a questionnaire to assess the overall quality of life of cancer patients. Participant responses to the questions regarding GHS ("How would you rate your overall health during the past week?") and QOL ("How would you rate your overall quality of life during the past week?") were scored on a 7-point scale (1=Very poor to 7=Excellent). Using linear transformation, raw scores were standardized, so that scores range from 0 to 100. The change from baseline in GHS (Item 29) and QOL (Item 30) combined score is presented (higher score=better outcome). Final analysis for this secondary outcome measure was performed with an analysis data cut-off date of 26-Jul-2021, as specified in the Supplemental Statistical Analysis Plan (sSAP). All participants who were randomized and received at least one dose of study treatment prior to the primary completion analysis data cut-off and who also had data available from at least 1 EORTC QLQ-C30 GHS & QOL assessment were analyzed.

End point type	Secondary

End point timeframe:

Baseline and Week 11

End point values	Pembrolizumab + Lenvatinib	Pembrolizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	240	231		
Units: Scores on a scale				
least squares mean (confidence interval 95%)	0.73 (-2.63 to 4.09)	3.79 (0.47 to 7.12)		

Statistical analyses

Statistical analysis title	Change from Baseline: EORTC QLQ-C30 GHS & QOL

Statistical analysis description:

Change from baseline to Week 11 in EORTC QLQ-C30 GHS & QOL combined score was compared between participants in the pembrolizumab + lenvatinib arm and participants in the pembrolizumab + placebo arm. Comparison was based on a constrained longitudinal data analysis (cLDA) model with the PRO scores as the response variable with covariates for treatment by study visit interaction, and stratification factors by chemotherapy ineligibility, PD-L1 CPS, and ECOG PS.

Comparison groups	Pembrolizumab + Lenvatinib v Pembrolizumab + Placebo
Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.182 [3]
Method	cLDA model
Parameter estimate	Difference in least squares means
Point estimate	-3.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.57
upper limit	1.44

Notes:

[3] - Two-sided p-value based on log rank test stratified on chemotherapy ineligibility, PD-L1 CPS, and ECOG PS.

Secondary: Time to True Deterioration (TTD) Based on Change from Baseline in EORTC QLQ-C30 GHS (Item 29) and QOL (Item 30) Combined Score

End point title	Time to True Deterioration (TTD) Based on Change from Baseline in EORTC QLQ-C30 GHS (Item 29) and QOL (Item 30) Combined Score

End point description:

TTD was defined as the time from baseline to the first onset of a ≥10-point decrease from the baseline EORTC QLQ-C30 GHS (Item 29) & QOL (Item 30) combined score. The EORTC QLQ-C30 questionnaire assesses overall patient quality of life. Responses about GHS & QOL were scored on a 7-point scale (1=Very poor to 7=Excellent). Raw scores were standardized to range from 0 to 100. The TTD is presented (longer TTD = better outcome). Final analysis for this secondary outcome measure was performed with an analysis data cut-off date of 26-Jul-2021, specified in the sSAP. All participants who were randomized and received ≥1 dose of study treatment prior to the primary completion analysis data cut-off and who also had data available from baseline and ≥1 post-baseline GHS & QOL assessments were analyzed. 9999=Upper limit not reached at time of data cut-off due to insufficient number of participants having the first onset of a ≥10-point decrease from baseline in GHS & QOL combined score.

End point type	Secondary

End point timeframe:

Baseline and up to approximately 25 months

End point values	Pembrolizumab + Lenvatinib	Pembrolizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	233	226		
Units: Months				
median (confidence interval 95%)	3.4 (2.1 to 4.3)	7.6 (4.2 to 9999)		

Statistical analyses

Statistical analysis title	TTD of EORTC QLQ-C30 GHS & QOL

Statistical analysis description:

TDD of EORTC QLQ-C30 GHS & QOL combined score was compared between the participants in the pembrolizumab + lenvatinib arm and the participants in the pembrolizumab + placebo arm. Comparison was based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by chemotherapy ineligibility, PD-L1 CPS, and ECOG PS.

Comparison groups	Pembrolizumab + Lenvatinib v Pembrolizumab + Placebo
Number of subjects included in analysis	459
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0005 [4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.24
upper limit	2.16

Notes:

[4] - Two-sided p-value based on log rank test stratified on chemotherapy ineligibility, PD-L1 CPS, and ECOG PS.

Secondary: Number of Participants who Experience an AE

End point title	Number of Participants who Experience an AE

End point description:

An AE was 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 could 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 experienced an AE is presented. Final analysis for this secondary outcome measure was performed with an analysis data cut-off date of 26-Jul-2021. All participants who were randomized and received at least one dose of study treatment prior to the primary completion analysis data cut-off were analyzed.

End point type	Secondary

End point timeframe:

Up to approximately 25 months

End point values	Pembrolizumab + Lenvatinib	Pembrolizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	241	242		
Units: Participants	234	235		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

An AE was 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 could 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 study treatment due to an AE is presented. Final analysis for this secondary outcome measure was performed with an analysis data cut-off date of 26-Jul-2021. All participants who were randomized and received at least one dose of study treatment prior to the primary completion analysis data cut-off were analyzed.

End point type	Secondary

End point timeframe:

Up to approximately 25 months

End point values	Pembrolizumab + Lenvatinib	Pembrolizumab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	241	242		
Units: Participants	83	44		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 52 months

Adverse event reporting additional description:

All-Cause Mortality (ACM): all randomized participants. AEs: all randomized participants who got ≥1 dose of study drug. Per protocol, MedDRA preferred terms "Neoplasm progression" (NP), "Malignant NP" and "Disease progression" not related to study drug are omitted as AEs. ACM and AEs are reported separately for pembrolizumab second course.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups

Reporting group title	Pembrolizumab + Lenvatinib First Course

Reporting group description:

Participants received pembrolizumab 200 mg via IV infusion on Day 1 of each 21-day cycle for up to 35 cycles (up to approximately 2 years) PLUS lenvatinib 20 mg via oral capsule QD until PD or discontinuation. With protocol amendment 3 (effective: 24-Sep-2021), participants discontinued lenvatinib.

Reporting group title	Pembrolizumab + Placebo Pembrolizumab Second Course

Reporting group description:

At the investigator's discretion, eligible participants randomized to the pembrolizumab PLUS placebo arm who completed the first course of pembrolizumab, or who had stopped pembrolizumab due to confirmed CR, initiated a second course of pembrolizumab (200 mg IV infusion on Day 1 of each 21-day cycle, for up to 17 cycles [up to approximately 1 additional year]) upon experiencing PD.

Reporting group title	Pembrolizumab + Lenvatinib Pembrolizumab Second Course

Reporting group description:

At the investigator's discretion, eligible participants randomized to the pembrolizumab PLUS lenvatinib arm who completed the first course of pembrolizumab, or who had stopped pembrolizumab due to confirmed CR, initiated a second course of pembrolizumab (200 mg IV infusion on Day 1 of each 21-day cycle, for up to 17 cycles [up to approximately 1 additional year]) upon experiencing PD.

Reporting group title	Pembrolizumab + Placebo First Course

Reporting group description:

Participants received pembrolizumab 200 mg via IV infusion on Day 1 of each 21-day cycle for up to 35 cycles (up to approximately 2 years) PLUS placebo for lenvatinib via oral capsule QD until PD or discontinuation.
With protocol amendment 3 (effective: 24-Sep-2021), participants discontinued placebo.

Serious adverse events	Pembrolizumab + Lenvatinib First Course	Pembrolizumab + Placebo Pembrolizumab Second Course	Pembrolizumab + Lenvatinib Pembrolizumab Second Course
Total subjects affected by serious adverse events			
subjects affected / exposed	155 / 247 (62.75%)	0 / 5 (0.00%)	0 / 2 (0.00%)
number of deaths (all causes)	178	0	0
number of deaths resulting from adverse events	49	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			

subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Bladder neoplasm			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cancer pain			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour pain			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parathyroid tumour benign			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic carcinoma			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Blood pressure fluctuation			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolism			

subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	4 / 247 (1.62%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	4 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iliac artery stenosis			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular stenosis			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	7 / 247 (2.83%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 7	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 7	0 / 0	0 / 0
General physical health deterioration			

subjects affected / exposed	4 / 247 (1.62%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Hernia			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperthermia			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired healing			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	4 / 247 (1.62%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	3 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	3 / 247 (1.21%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			

subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	2 / 247 (0.81%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	2 / 247 (0.81%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic pain			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			

subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cough			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	5 / 247 (2.02%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	5 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	2 / 2	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Psychiatric disorders			
Delirium			

subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Lead dislodgement			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device occlusion			
subjects affected / exposed	2 / 247 (0.81%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device dislocation			
subjects affected / exposed	2 / 247 (0.81%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic enzymes increased			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SARS-CoV-2 test positive			

subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	4 / 247 (1.62%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	3 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 247 (0.81%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical vertebral fracture			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	2 / 247 (0.81%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular access site occlusion			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple injuries			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Subdural haematoma			

subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thermal burn			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract stoma complication			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound haematoma			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	4 / 247 (1.62%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 4	0 / 0	0 / 0
Acute coronary syndrome			

subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	5 / 247 (2.02%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	3 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	2 / 247 (0.81%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Prinzmetal angina			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiopulmonary failure			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			

subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ataxia			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parkinsonism			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myasthenia gravis			

subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic encephalopathy			
subjects affected / exposed	2 / 247 (0.81%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	2 / 247 (0.81%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic stroke			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial nerve disorder			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			

subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	2 / 247 (0.81%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 247 (1.21%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Colitis			
subjects affected / exposed	3 / 247 (1.21%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis microscopic			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ulcerative			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal fistula			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	2 / 247 (0.81%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	4 / 247 (1.62%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	5 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticular perforation			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal obstruction			

subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	4 / 247 (1.62%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterovesical fistula			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	2 / 247 (0.81%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Intestinal haemorrhage			

subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal haemorrhage			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mechanical ileus			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstructive pancreatitis			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	3 / 247 (1.21%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune-mediated enterocolitis			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			

subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal fistula			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholangitis acute			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	2 / 247 (0.81%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	2 / 247 (0.81%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis acute			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatotoxicity			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune-mediated hepatitis			

subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice cholestatic			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver disorder			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash papular			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stevens-Johnson syndrome			
subjects affected / exposed	2 / 247 (0.81%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash maculo-papular			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	12 / 247 (4.86%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 17	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Bladder mass			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proteinuria			

subjects affected / exposed	3 / 247 (1.21%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postrenal failure			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Perinephric collection			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	3 / 247 (1.21%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	6 / 247 (2.43%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	2 / 7	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic kidney disease			
subjects affected / exposed	2 / 247 (0.81%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Bladder obstruction			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephritis			

subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary bladder haemorrhage			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract obstruction			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophysitis			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperthyroidism			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			

Bone lesion			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myositis			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteitis			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pathological fracture			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polymyalgia rheumatica			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sacral pain			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthralgia			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			

subjects affected / exposed	2 / 247 (0.81%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalitis			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis perforated			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atypical pneumonia			

subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	4 / 247 (1.62%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
COVID-19 pneumonia			
subjects affected / exposed	5 / 247 (2.02%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 0
Campylobacter infection			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Perirectal abscess			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic abscess			

subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	14 / 247 (5.67%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	2 / 14	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 5	0 / 0	0 / 0
Kidney infection			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious pleural effusion			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver abscess			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract candidiasis			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			

subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	3 / 247 (1.21%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 2	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	2 / 247 (0.81%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	2 / 247 (0.81%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	4 / 247 (1.62%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 0
Urinary tract infection			

subjects affected / exposed	9 / 247 (3.64%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 9	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Urinary tract infection bacterial			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	2 / 247 (0.81%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	3 / 247 (1.21%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	3 / 247 (1.21%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	4 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cachexia			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Failure to thrive			
subjects affected / exposed	0 / 247 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			

subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	2 / 247 (0.81%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic acidosis			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperuricaemia			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	1 / 247 (0.40%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Pembrolizumab + Placebo First Course		

Total subjects affected by serious adverse events			
subjects affected / exposed	116 / 254 (45.67%)		
number of deaths (all causes)	175		
number of deaths resulting from adverse events	26		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	0 / 254 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bladder neoplasm			
subjects affected / exposed	0 / 254 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cancer pain			
subjects affected / exposed	1 / 254 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tumour pain			
subjects affected / exposed	1 / 254 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Parathyroid tumour benign			
subjects affected / exposed	0 / 254 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancreatic carcinoma			
subjects affected / exposed	1 / 254 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung neoplasm malignant			
subjects affected / exposed	1 / 254 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			

Blood pressure fluctuation			
subjects affected / exposed	0 / 254 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Embolism			
subjects affected / exposed	2 / 254 (0.79%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Hypertension			
subjects affected / exposed	0 / 254 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	2 / 254 (0.79%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Iliac artery stenosis			
subjects affected / exposed	0 / 254 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 254 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular stenosis			
subjects affected / exposed	0 / 254 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Deep vein thrombosis			
subjects affected / exposed	1 / 254 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			

Death				
subjects affected / exposed	3 / 254 (1.18%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 3			
General physical health deterioration				
subjects affected / exposed	2 / 254 (0.79%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Hernia				
subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyperthermia				
subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Impaired healing				
subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	2 / 254 (0.79%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Multiple organ dysfunction syndrome				
subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Asthenia				
subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Chest pain				

subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Malaise				
subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oedema peripheral				
subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	4 / 254 (1.57%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Vaginal haemorrhage				
subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pelvic pain				
subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Haemoptysis				
subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			

Chronic obstructive pulmonary disease				
subjects affected / exposed	4 / 254 (1.57%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Cough				
subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	3 / 254 (1.18%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Pneumothorax				
subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Pneumonitis				
subjects affected / exposed	3 / 254 (1.18%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 1			
Pleural effusion				
subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Interstitial lung disease				
subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				

Delirium			
subjects affected / exposed	0 / 254 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Confusional state			
subjects affected / exposed	0 / 254 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Product issues			
Lead dislodgement			
subjects affected / exposed	1 / 254 (0.39%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Device occlusion			
subjects affected / exposed	0 / 254 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Device dislocation			
subjects affected / exposed	3 / 254 (1.18%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 254 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood creatinine increased			
subjects affected / exposed	1 / 254 (0.39%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatic enzymes increased			
subjects affected / exposed	1 / 254 (0.39%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

SARS-CoV-2 test positive			
subjects affected / exposed	2 / 254 (0.79%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Platelet count decreased			
subjects affected / exposed	0 / 254 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 254 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cervical vertebral fracture			
subjects affected / exposed	1 / 254 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Femoral neck fracture			
subjects affected / exposed	2 / 254 (0.79%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Femur fracture			
subjects affected / exposed	1 / 254 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular access site occlusion			
subjects affected / exposed	0 / 254 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Multiple injuries			
subjects affected / exposed	0 / 254 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Subdural haematoma				
subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Thermal burn				
subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract stoma complication				
subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hip fracture				
subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Wound haematoma				
subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Atrial fibrillation				
subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial flutter				
subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acute coronary syndrome				

subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cardiac failure				
subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cardio-respiratory arrest				
subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Coronary artery disease				
subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	2 / 254 (0.79%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Prinzmetal angina				
subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tachycardia				
subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiopulmonary failure				
subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Ventricular tachycardia				

subjects affected / exposed	1 / 254 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	0 / 254 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dizziness			
subjects affected / exposed	0 / 254 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular accident			
subjects affected / exposed	2 / 254 (0.79%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Cerebral infarction			
subjects affected / exposed	3 / 254 (1.18%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 2		
Ataxia			
subjects affected / exposed	0 / 254 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 254 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Parkinsonism			
subjects affected / exposed	0 / 254 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myasthenia gravis			

subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolic encephalopathy				
subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Loss of consciousness				
subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ischaemic stroke				
subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemorrhagic stroke				
subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Facial nerve disorder				
subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Epilepsy				
subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sciatica				

subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Somnolence				
subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal cord compression				
subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				
subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	6 / 254 (2.36%)			
occurrences causally related to treatment / all	1 / 6			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				
subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ear and labyrinth disorders				
Vertigo				
subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				

Colitis			
subjects affected / exposed	3 / 254 (1.18%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Colitis microscopic			
subjects affected / exposed	0 / 254 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colitis ulcerative			
subjects affected / exposed	1 / 254 (0.39%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Anal fistula			
subjects affected / exposed	1 / 254 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	0 / 254 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	0 / 254 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 254 (0.39%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Diverticular perforation			
subjects affected / exposed	0 / 254 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Duodenal obstruction			

subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Ileus				
subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dysphagia				
subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Enterovesical fistula				
subjects affected / exposed	2 / 254 (0.79%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gastric ulcer				
subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Duodenal ulcer haemorrhage				
subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Intestinal haemorrhage				

subjects affected / exposed	0 / 254 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Large intestinal haemorrhage			
subjects affected / exposed	0 / 254 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Mechanical ileus			
subjects affected / exposed	0 / 254 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 254 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Obstructive pancreatitis			
subjects affected / exposed	0 / 254 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			
subjects affected / exposed	0 / 254 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			
subjects affected / exposed	2 / 254 (0.79%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Immune-mediated enterocolitis			
subjects affected / exposed	0 / 254 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Inguinal hernia			

subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal fistula				
subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Stomatitis				
subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholangitis acute				
subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholecystitis				
subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholecystitis acute				
subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatitis acute				
subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatotoxicity				
subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Immune-mediated hepatitis				

subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Jaundice cholestatic				
subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Liver disorder				
subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Rash papular				
subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Stevens-Johnson syndrome				
subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rash maculo-papular				
subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute kidney injury				
subjects affected / exposed	5 / 254 (1.97%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 1			
Bladder mass				
subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Proteinuria				

subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Postrenal failure				
subjects affected / exposed	2 / 254 (0.79%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Perinephric collection				
subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal failure				
subjects affected / exposed	3 / 254 (1.18%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	1 / 2			
Hydronephrosis				
subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haematuria				
subjects affected / exposed	5 / 254 (1.97%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Chronic kidney disease				
subjects affected / exposed	2 / 254 (0.79%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Bladder obstruction				
subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nephritis				

subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary retention				
subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary bladder haemorrhage				
subjects affected / exposed	2 / 254 (0.79%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Renal impairment				
subjects affected / exposed	2 / 254 (0.79%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Urinary tract obstruction				
subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Endocrine disorders				
Hypothyroidism				
subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypophysitis				
subjects affected / exposed	2 / 254 (0.79%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Hyperthyroidism				
subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				

Bone lesion				
subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myositis				
subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Osteitis				
subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pain in extremity				
subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pathological fracture				
subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Polymyalgia rheumatica				
subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sacral pain				
subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Arthralgia				
subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Back pain				

subjects affected / exposed	1 / 254 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	0 / 254 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	0 / 254 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 254 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Encephalitis			
subjects affected / exposed	0 / 254 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			
subjects affected / exposed	0 / 254 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Appendicitis			
subjects affected / exposed	0 / 254 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Appendicitis perforated			
subjects affected / exposed	1 / 254 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atypical pneumonia			

subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
COVID-19				
subjects affected / exposed	2 / 254 (0.79%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
COVID-19 pneumonia				
subjects affected / exposed	2 / 254 (0.79%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Campylobacter infection				
subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumocystis jirovecii pneumonia				
subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peritonitis				
subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Perirectal abscess				
subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pelvic abscess				

subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	5 / 254 (1.97%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 2			
Kidney infection				
subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infectious pleural effusion				
subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Gastroenteritis				
subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Liver abscess				
subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract candidiasis				
subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin infection				

subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	4 / 254 (1.57%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 1			
Respiratory tract infection				
subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis acute				
subjects affected / exposed	2 / 254 (0.79%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				
subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Postoperative wound infection				
subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				

subjects affected / exposed	14 / 254 (5.51%)			
occurrences causally related to treatment / all	1 / 17			
deaths causally related to treatment / all	0 / 1			
Urinary tract infection bacterial				
subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	4 / 254 (1.57%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 1			
Metabolism and nutrition disorders				
Diabetic ketoacidosis				
subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dehydration				
subjects affected / exposed	2 / 254 (0.79%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Decreased appetite				
subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cachexia				
subjects affected / exposed	0 / 254 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Failure to thrive				
subjects affected / exposed	1 / 254 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypercalcaemia				

subjects affected / exposed	2 / 254 (0.79%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	0 / 254 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	0 / 254 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolic acidosis			
subjects affected / exposed	0 / 254 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperuricaemia			
subjects affected / exposed	0 / 254 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperkalaemia			
subjects affected / exposed	0 / 254 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	0 / 254 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	0 / 254 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Pembrolizumab + Lenvatinib First Course	Pembrolizumab + Placebo Pembrolizumab Second Course	Pembrolizumab + Lenvatinib Pembrolizumab Second Course
Total subjects affected by non-serious adverse events			
subjects affected / exposed	238 / 247 (96.36%)	5 / 5 (100.00%)	1 / 2 (50.00%)
Vascular disorders			
Hypotension			
subjects affected / exposed	10 / 247 (4.05%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences (all)	12	0	0
Hypertension			
subjects affected / exposed	99 / 247 (40.08%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences (all)	125	0	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	25 / 247 (10.12%)	1 / 5 (20.00%)	0 / 2 (0.00%)
occurrences (all)	33	1	0
Oedema peripheral			
subjects affected / exposed	28 / 247 (11.34%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences (all)	31	0	0
Mucosal inflammation			
subjects affected / exposed	20 / 247 (8.10%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences (all)	21	0	0
Fatigue			
subjects affected / exposed	52 / 247 (21.05%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences (all)	58	0	0
Asthenia			
subjects affected / exposed	52 / 247 (21.05%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences (all)	62	0	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	20 / 247 (8.10%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences (all)	21	0	0
Dysphonia			

subjects affected / exposed	40 / 247 (16.19%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences (all)	49	0	0
Cough			
subjects affected / exposed	11 / 247 (4.45%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences (all)	12	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	12 / 247 (4.86%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences (all)	12	0	0
Investigations			
Amylase increased			
subjects affected / exposed	24 / 247 (9.72%)	1 / 5 (20.00%)	0 / 2 (0.00%)
occurrences (all)	33	1	0
Alanine aminotransferase increased			
subjects affected / exposed	22 / 247 (8.91%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences (all)	29	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	21 / 247 (8.50%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences (all)	25	0	0
Blood creatinine increased			
subjects affected / exposed	28 / 247 (11.34%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences (all)	33	0	0
Blood creatine phosphokinase increased			
subjects affected / exposed	4 / 247 (1.62%)	2 / 5 (40.00%)	0 / 2 (0.00%)
occurrences (all)	5	5	0
Blood alkaline phosphatase increased			
subjects affected / exposed	19 / 247 (7.69%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences (all)	21	0	0
Blood urea increased			
subjects affected / exposed	2 / 247 (0.81%)	1 / 5 (20.00%)	0 / 2 (0.00%)
occurrences (all)	2	1	0
Weight decreased			
subjects affected / exposed	50 / 247 (20.24%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences (all)	51	0	0
Platelet count decreased			

subjects affected / exposed	16 / 247 (6.48%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences (all)	23	0	0
Lipase increased			
subjects affected / exposed	39 / 247 (15.79%)	1 / 5 (20.00%)	0 / 2 (0.00%)
occurrences (all)	49	1	0
Injury, poisoning and procedural complications			
Thermal burn			
subjects affected / exposed	0 / 247 (0.00%)	1 / 5 (20.00%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	21 / 247 (8.50%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences (all)	25	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	48 / 247 (19.43%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences (all)	57	0	0
Eye disorders			
Xerophthalmia			
subjects affected / exposed	0 / 247 (0.00%)	1 / 5 (20.00%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	65 / 247 (26.32%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences (all)	111	0	0
Abdominal pain upper			
subjects affected / exposed	14 / 247 (5.67%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences (all)	17	0	0
Abdominal pain			
subjects affected / exposed	25 / 247 (10.12%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences (all)	32	0	0
Haemorrhoids			
subjects affected / exposed	6 / 247 (2.43%)	0 / 5 (0.00%)	1 / 2 (50.00%)
occurrences (all)	6	0	1
Nausea			

subjects affected / exposed	52 / 247 (21.05%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences (all)	65	0	0
Stomatitis			
subjects affected / exposed	18 / 247 (7.29%)	1 / 5 (20.00%)	0 / 2 (0.00%)
occurrences (all)	23	1	0
Vomiting			
subjects affected / exposed	37 / 247 (14.98%)	1 / 5 (20.00%)	0 / 2 (0.00%)
occurrences (all)	42	1	0
Constipation			
subjects affected / exposed	40 / 247 (16.19%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences (all)	50	0	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	38 / 247 (15.38%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences (all)	52	0	0
Pruritus			
subjects affected / exposed	34 / 247 (13.77%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences (all)	41	0	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	25 / 247 (10.12%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences (all)	29	0	0
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	14 / 247 (5.67%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences (all)	22	0	0
Proteinuria			
subjects affected / exposed	101 / 247 (40.89%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences (all)	149	0	0
Haematuria			
subjects affected / exposed	32 / 247 (12.96%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences (all)	36	0	0
Chronic kidney disease			
subjects affected / exposed	3 / 247 (1.21%)	1 / 5 (20.00%)	0 / 2 (0.00%)
occurrences (all)	3	1	0
Endocrine disorders			

Hyperthyroidism			
subjects affected / exposed	16 / 247 (6.48%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences (all)	17	0	0
Hypothyroidism			
subjects affected / exposed	98 / 247 (39.68%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences (all)	109	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	25 / 247 (10.12%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences (all)	27	0	0
Arthralgia			
subjects affected / exposed	27 / 247 (10.93%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences (all)	38	0	0
Myalgia			
subjects affected / exposed	13 / 247 (5.26%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences (all)	14	0	0
Pain in extremity			
subjects affected / exposed	14 / 247 (5.67%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences (all)	15	0	0
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	54 / 247 (21.86%)	2 / 5 (40.00%)	0 / 2 (0.00%)
occurrences (all)	75	2	0
Upper respiratory tract infection			
subjects affected / exposed	8 / 247 (3.24%)	1 / 5 (20.00%)	0 / 2 (0.00%)
occurrences (all)	8	1	0
Gastrointestinal infection			
subjects affected / exposed	0 / 247 (0.00%)	1 / 5 (20.00%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Cystitis			
subjects affected / exposed	3 / 247 (1.21%)	1 / 5 (20.00%)	0 / 2 (0.00%)
occurrences (all)	3	1	0
Metabolism and nutrition disorders			
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 247 (0.40%)	1 / 5 (20.00%)	0 / 2 (0.00%)
occurrences (all)	1	1	0

Hyponatraemia			
subjects affected / exposed	18 / 247 (7.29%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences (all)	21	0	0
Hypoalbuminaemia			
subjects affected / exposed	19 / 247 (7.69%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences (all)	22	0	0
Hyperkalaemia			
subjects affected / exposed	9 / 247 (3.64%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences (all)	12	0	0
Hyperglycaemia			
subjects affected / exposed	12 / 247 (4.86%)	1 / 5 (20.00%)	0 / 2 (0.00%)
occurrences (all)	12	1	0
Hypercholesterolaemia			
subjects affected / exposed	3 / 247 (1.21%)	1 / 5 (20.00%)	0 / 2 (0.00%)
occurrences (all)	3	1	0
Decreased appetite			
subjects affected / exposed	68 / 247 (27.53%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences (all)	85	0	0

Non-serious adverse events	Pembrolizumab + Placebo First Course		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	236 / 254 (92.91%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	13 / 254 (5.12%)		
occurrences (all)	15		
Hypertension			
subjects affected / exposed	23 / 254 (9.06%)		
occurrences (all)	33		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	35 / 254 (13.78%)		
occurrences (all)	47		
Oedema peripheral			
subjects affected / exposed	26 / 254 (10.24%)		
occurrences (all)	27		

Mucosal inflammation subjects affected / exposed occurrences (all)	9 / 254 (3.54%) 9		
Fatigue subjects affected / exposed occurrences (all)	53 / 254 (20.87%) 55		
Asthenia subjects affected / exposed occurrences (all)	33 / 254 (12.99%) 46		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea subjects affected / exposed occurrences (all)	15 / 254 (5.91%) 20		
Dysphonia subjects affected / exposed occurrences (all)	2 / 254 (0.79%) 2		
Cough subjects affected / exposed occurrences (all)	20 / 254 (7.87%) 26		
Psychiatric disorders			
Insomnia subjects affected / exposed occurrences (all)	17 / 254 (6.69%) 18		
Investigations			
Amylase increased subjects affected / exposed occurrences (all)	27 / 254 (10.63%) 39		
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	15 / 254 (5.91%) 19		
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	17 / 254 (6.69%) 20		
Blood creatinine increased subjects affected / exposed occurrences (all)	19 / 254 (7.48%) 27		

Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	11 / 254 (4.33%) 16		
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	16 / 254 (6.30%) 16		
Blood urea increased subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 2		
Weight decreased subjects affected / exposed occurrences (all)	23 / 254 (9.06%) 24		
Platelet count decreased subjects affected / exposed occurrences (all)	7 / 254 (2.76%) 10		
Lipase increased subjects affected / exposed occurrences (all)	28 / 254 (11.02%) 40		
Injury, poisoning and procedural complications Thermal burn subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	14 / 254 (5.51%) 16		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	64 / 254 (25.20%) 74		
Eye disorders Xerophthalmia subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0		
Gastrointestinal disorders			

Diarrhoea subjects affected / exposed occurrences (all)	51 / 254 (20.08%) 75		
Abdominal pain upper subjects affected / exposed occurrences (all)	11 / 254 (4.33%) 12		
Abdominal pain subjects affected / exposed occurrences (all)	23 / 254 (9.06%) 26		
Haemorrhoids subjects affected / exposed occurrences (all)	2 / 254 (0.79%) 2		
Nausea subjects affected / exposed occurrences (all)	44 / 254 (17.32%) 53		
Stomatitis subjects affected / exposed occurrences (all)	7 / 254 (2.76%) 10		
Vomiting subjects affected / exposed occurrences (all)	26 / 254 (10.24%) 31		
Constipation subjects affected / exposed occurrences (all)	38 / 254 (14.96%) 45		
Skin and subcutaneous tissue disorders			
Rash subjects affected / exposed occurrences (all)	27 / 254 (10.63%) 33		
Pruritus subjects affected / exposed occurrences (all)	48 / 254 (18.90%) 64		
Palmar-plantar erythrodysaesthesia syndrome subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 1		
Renal and urinary disorders			

Renal impairment subjects affected / exposed occurrences (all) Proteinuria subjects affected / exposed occurrences (all) Haematuria subjects affected / exposed occurrences (all) Chronic kidney disease subjects affected / exposed occurrences (all)	9 / 254 (3.54%) 11 71 / 254 (27.95%) 94 32 / 254 (12.60%) 47 6 / 254 (2.36%) 9		
Endocrine disorders Hyperthyroidism subjects affected / exposed occurrences (all) Hypothyroidism subjects affected / exposed occurrences (all)	12 / 254 (4.72%) 13 27 / 254 (10.63%) 30		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	21 / 254 (8.27%) 24 26 / 254 (10.24%) 31 4 / 254 (1.57%) 4 10 / 254 (3.94%) 10		
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	46 / 254 (18.11%) 66		

Upper respiratory tract infection subjects affected / exposed occurrences (all)	7 / 254 (2.76%) 10		
Gastrointestinal infection subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0		
Cystitis subjects affected / exposed occurrences (all)	8 / 254 (3.15%) 9		
Metabolism and nutrition disorders Type 2 diabetes mellitus subjects affected / exposed occurrences (all)	1 / 254 (0.39%) 2		
Hyponatraemia subjects affected / exposed occurrences (all)	17 / 254 (6.69%) 19		
Hypoalbuminaemia subjects affected / exposed occurrences (all)	12 / 254 (4.72%) 12		
Hyperkalaemia subjects affected / exposed occurrences (all)	16 / 254 (6.30%) 18		
Hyperglycaemia subjects affected / exposed occurrences (all)	12 / 254 (4.72%) 15		
Hypercholesterolaemia subjects affected / exposed occurrences (all)	0 / 254 (0.00%) 0		
Decreased appetite subjects affected / exposed occurrences (all)	43 / 254 (16.93%) 51		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 August 2019	Major changes of Amendment 1 included, based on support from the current literature, use of this class of drugs in a higher age range for this patient population.
12 October 2021	Major changes of Amendment 3 included: 1) updating the dose modification and toxicity management guidelines for infusion reaction AEs, 2) making updates consistent with recommendations of the external Data Monitoring Committee after an interim review of the data; specifically, that all participants be unblinded and lenvatinib and placebo administration stopped, and 3) allowing the study to remain open so that participants still on study could have continued access to pembrolizumab.
14 February 2023	Major changes of Amendment 4 included reducing the scope of the study such that: 1) long-term efficacy/survival data were no longer be collected; therefore, upon either completion or discontinuation of pembrolizumab, participants had a final Safety Follow-up visit and were discontinued from the study, 2) participants in Efficacy Follow-up stopped efficacy assessments and were discontinued from the study, and 3) participants in Survival Follow-up were considered to have completed the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported