Clinical trial results:
A Phase 3, Multinational, Randomized, Open-Label, Parallel-Arm study of Avelumab (MSB0010718C) in Combination With Axitinib (Inlyta) Versus Sunitinib (Sutent) Monotherapy in the First-Line Treatment of Patients With Advanced Renal Cell Carcinoma

Summary

EudraCT number	2015-002429-20
Trial protocol	NL FR SE BE GB DE HU AT DK ES IT
Global end of trial date	26 June 2024

Results information

Result version number	v1 (current)
This version publication date	10 July 2025
First version publication date	10 July 2025

Trial information

Trial identification

Sponsor protocol code	B9991003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02684006
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	66 Hudson Boulevard East, New York, United States, NY 10001-2192
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.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 June 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 June 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that avelumab in combination with axitinib is superior to sunitinib monotherapy in prolonging progression free survival (PFS) or overall survival (OS) in the first-line treatment of programmed death-ligand 1 (PD-L1) positive participants with advanced renal cell carcinoma (aRCC).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trials participants were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 March 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	99 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 5
Country: Number of subjects enrolled	France: 70
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	Israel: 41
Country: Number of subjects enrolled	Italy: 15
Country: Number of subjects enrolled	Japan: 67
Country: Number of subjects enrolled	Korea, Republic of: 48
Country: Number of subjects enrolled	Mexico: 12
Country: Number of subjects enrolled	Netherlands: 38
Country: Number of subjects enrolled	New Zealand: 9
Country: Number of subjects enrolled	Romania: 20
Country: Number of subjects enrolled	Russian Federation: 138
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	United Kingdom: 32
Country: Number of subjects enrolled	United States: 261
Country: Number of subjects enrolled	Australia: 32

Country: Number of subjects enrolled	Austria: 5
Country: Number of subjects enrolled	Belgium: 9
Country: Number of subjects enrolled	Canada: 74
Worldwide total number of subjects	886
EEA total number of subjects	172

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)	546
From 65 to 84 years	336
85 years and over	4

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 886 participants were enrolled and randomized in the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Avelumab + Axitinib

Arm description:

Participants with advanced renal cell carcinoma (aRCC) received avelumab 10 milligram per kilogram (mg/kg), intravenously (IV) once every two weeks (Q2W) in a 6-week cycle plus axitinib 5 mg, orally twice daily (BID). Each treatment cycle was of 42 days.

Arm type	Experimental
Investigational medicinal product name	Axitinib 5 mg
Investigational medicinal product code	AG-013736
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received Axitinib 5 mg twice daily administered 12 hours apart orally.

Investigational medicinal product name	Avelumab 10mg
Investigational medicinal product code	MSB0010718C
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received Avelumab 10 mg/kg intravenously once every two weeks of each 42-day cycle

Arm title	Sunitinib

Arm description:

Participants with aRCC received sunitinib 50 mg orally, QD on a schedule of 4 weeks on treatment followed by 2 weeks off treatment (schedule 4/2 in 6-week cycles). Each treatment cycle was of 42 days.

Arm type	Experimental
Investigational medicinal product name	Sunitinib 50 mg
Investigational medicinal product code	SU011248
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received Sunitinib 50 mg once daily orally

Number of subjects in period 1	Avelumab + Axitinib	Sunitinib
Started	442	444
Completed	0	0
Not completed	442	444
Adverse event, serious fatal	25	22
Physician decision	15	8
Consent withdrawn by subject	29	43
Global deterioration of health status	18	20
Adverse event, non-fatal	86	65
No longer met eligibility criteria	6	2
Non-compliance with study drug	1	1
Unspecified	18	6
Progressive disease	236	266
Lost to follow-up	-	1
Protocol deviation	2	1
Participation terminated by sponsor	6	9

Baseline characteristics

Reporting groups	
Reporting group title	Avelumab + Axitinib
Reporting group description:	
Participants with advanced renal cell carcinoma (aRCC) received avelumab 10 milligram per kilogram (mg/kg), intravenously (IV) once every two weeks (Q2W) in a 6-week cycle plus axitinib 5 mg, orally twice daily (BID). Each treatment cycle was of 42 days.	
Reporting group title	Sunitinib
Reporting group description:	
Participants with aRCC received sunitinib 50 mg orally, QD on a schedule of 4 weeks on treatment followed by 2 weeks off treatment (schedule 4/2 in 6-week cycles). Each treatment cycle was of 42 days.	

Reporting group values	Avelumab + Axitinib	Sunitinib	Total
Number of subjects	442	444	886
Age Categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	60.86	60.66	
standard deviation	± 9.95	± 10.28	-
Gender categorical Units: Subjects			
Male	316	344	660
Female	126	100	226
Ethnicity Units: Subjects			
Hispanic or Latino	19	18	37
Not Hispanic or Latino	388	377	765
Unknown or Not Reported	35	49	84
Race Units: Subjects			
American Indian or Alaska Native	4	4	8
Asian	70	63	133
Native Hawaiian or Other Pacific Islander	0	1	1
Black or African American	10	10	20
White	332	334	666
Unknown or Not Reported	26	32	58

End points

End points reporting groups

Reporting group title	Avelumab + Axitinib

Reporting group description:

Participants with advanced renal cell carcinoma (aRCC) received avelumab 10 milligram per kilogram (mg/kg), intravenously (IV) once every two weeks (Q2W) in a 6-week cycle plus axitinib 5 mg, orally twice daily (BID). Each treatment cycle was of 42 days.

Reporting group title	Sunitinib

Reporting group description:

Participants with aRCC received sunitinib 50 mg orally, QD on a schedule of 4 weeks on treatment followed by 2 weeks off treatment (schedule 4/2 in 6-week cycles). Each treatment cycle was of 42 days.

Primary: Progression Free Survival (PFS) as Assessed by Blinded Independent Central Review (BICR) in Programmed Death-Ligand 1 (PD-L1) Positive Participants

End point title	Progression Free Survival (PFS) as Assessed by Blinded Independent Central Review (BICR) in Programmed Death-Ligand 1 (PD-L1) Positive Participants

End point description:

PFS: time from date of randomization to date of first documentation of progressive disease (PD) according to Response Evaluation Criteria in Solid Tumours (RECIST version [v] 1.1) or death due to any cause, whichever occurred first as assessed by BICR. PFS data was censored on date of last adequate tumor assessment for participants who did not have an event (PD/death), who started new anti-cancer therapy prior to an event or for participants with an event after 2/more missing tumor assessments. PD: at least 20%, increase in sum of all longest diameter of target lesions, taking as reference smallest sum on study. In addition to relative increase of 20%, sum must have also demonstrated an absolute more than (>) of at least 5 millimeter (mm). FAS included all participants who were randomized. Analysis was performed on subset of randomized participants, who were PD-L1 positive. 99999 indicates upper limit of 95% CI was not estimable due to insufficient number of participants with event.

End point type	Primary

End point timeframe:

From date of randomization to the first documentation of PD or death due to any cause or censoring date, whichever occurred first (maximum up to approximately 26 months)

End point values	Avelumab + Axitinib	Sunitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	270	290		
Units: Months				
median (confidence interval 95%)	13.8 (11.1 to 99999)	7.2 (5.7 to 9.7)		

Statistical analyses

Statistical analysis title	Avelumab + Axitinib versus Sunitinib
Comparison groups	Avelumab + Axitinib v Sunitinib

Number of subjects included in analysis	560
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.0001 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.475
upper limit	0.79

Notes:

[1] - 2-sided p-value

[2] - 2-sided p-value

Primary: Overall Survival (OS) in PD-L1 Positive Participants

End point title	Overall Survival (OS) in PD-L1 Positive Participants

End point description:

OS was defined as the time from the date of randomization to the date of death due to any cause. Participants last known to be alive were censored at date of last contact. Analysis was performed using Kaplan-Meier method. FAS included all participants who are randomized. Analysis was performed on subset of randomized participants, who were PD-L1 positive.

End point type	Primary

End point timeframe:

From the date of randomization to the date of death due to any cause or censoring date, whichever occurred first (maximum up to approximately 89 months)

End point values	Avelumab + Axitinib	Sunitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	270	290		
Units: Months				
median (confidence interval 95%)	43.2 (36.5 to 51.7)	36.2 (29.8 to 44.2)		

Statistical analyses

Statistical analysis title	Avelumab + Axitinib versus Sunitinib
Comparison groups	Avelumab + Axitinib v Sunitinib
Number of subjects included in analysis	560
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.1509 [4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.86

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.701
upper limit	1.057

Notes:

[3] - 2-sided p-value

[4] - 2-sided p-value

Secondary: PFS as Assessed by BICR in Participants Irrespective of PD-L1 Expression

End point title	PFS as Assessed by BICR in Participants Irrespective of PD-L1 Expression

End point description:

PFS: time from the date of randomization to the date of the first documentation of PD or death due to any cause, whichever occurred first as assessed by BICR. PFS data was censored on date of last adequate tumor assessment for participants who did not have an event (PD or death), who started new anti-cancer therapy prior to an event or for participants with an event after 2 or more missing tumor assessments. PD was defined as at least a 20% increase in the sum of all the longest diameter of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to relative increase of 20%, sum must have also demonstrated an absolute > of at least 5 mm. The appearance of one or more new lesions was also considered progression. FAS included all randomized participants. 99999 indicates upper limit of 95% CI was not estimable due to insufficient number of participants with event.

End point type	Secondary

End point timeframe:

From date of randomization to the first documentation of PD or death due to any cause or censoring date, whichever occurred first (maximum up to approximately 26 months)

End point values	Avelumab + Axitinib	Sunitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	442	444		
Units: Months				
median (confidence interval 95%)	13.8 (11.1 to 99999)	8.4 (6.9 to 11.1)		

Statistical analyses

Statistical analysis title	Avelumab + Axitinib versus Sunitinib
Comparison groups	Avelumab + Axitinib v Sunitinib
Number of subjects included in analysis	886
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.0002 [6]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.69

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.563
upper limit	0.84

Notes:

[5] - 2-sided p-value

[6] - 2-sided p-value

Secondary: OS in Participants Irrespective of PD-L1 Expression

End point title	OS in Participants Irrespective of PD-L1 Expression

End point description:

OS was defined as the time (in months) from the date of randomization to the date of death due to any cause. Participants last known to be alive were censored at date of last contact. Analysis was performed using Kaplan-Meier method. FAS included all randomized participants.

End point type	Secondary

End point timeframe:

From the date of randomization to the date of death due to any cause or censoring date, whichever occurred first (maximum up to approximately 89 months)

End point values	Avelumab + Axitinib	Sunitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	442	444		
Units: Months				
median (confidence interval 95%)	44.8 (39.7 to 51.1)	38.9 (31.4 to 45.2)		

Statistical analyses

Statistical analysis title	Avelumab + Axitinib versus Sunitinib
Comparison groups	Sunitinib v Avelumab + Axitinib
Number of subjects included in analysis	886
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.1338 [8]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.749
upper limit	1.039

Notes:

[7] - 2-sided p-value

[8] - 2-sided p-value

Secondary: Percentage of Participants With OR as Assessed by Investigator Irrespective of PD-L1 Expression

End point title	Percentage of Participants With OR as Assessed by Investigator Irrespective of PD-L1 Expression

End point description:

OR was defined as best overall response of CR or PR according to RECIST v1.1 as assessed by investigator recorded from date of randomization until disease progression. CR was defined as complete disappearance of all target and non-target lesions with the exception of nodal disease. All lymph nodes must decrease to normal size (short axis<10 mm). All target lesions must be assessed. PR was defined as greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. All target lesions must be assessed. 95% CI was based on Clopper-Pearson method. FAS included all randomized participants.

End point type	Secondary

End point timeframe:

From date of randomization until PD (maximum up to approximately 89 months)

End point values	Avelumab + Axitinib	Sunitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	442	444		
Units: Percentage of participants				
number (confidence interval 95%)	59.7 (55.0 to 64.3)	32.0 (27.7 to 36.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Objective Response (OR) as Assessed by BICR Irrespective of PD-L1 Expression

End point title	Percentage of Participants With Objective Response (OR) as Assessed by BICR Irrespective of PD-L1 Expression

End point description:

OR was defined as best overall response of complete response (CR) or partial response (PR) according to RECIST v1.1 as assessed by BICR recorded from date of randomization until disease progression. CR was defined as complete disappearance of all target and non-target lesions with the exception of nodal disease. All lymph nodes must decrease to normal size (short axis<10 mm). All target lesions must be assessed. PR was defined as greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. All target lesions must be assessed. 95% CI was based on Clopper-Pearson method. FAS included all randomized participants.

End point type	Secondary

End point timeframe:

From date of randomization until PD (maximum up to approximately 26 months)

End point values	Avelumab + Axitinib	Sunitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	442	444		
Units: Percentage of participants				
number (confidence interval 95%)	51.4 (46.6 to 56.1)	25.7 (21.7 to 30.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With DC as Assessed by Investigator Irrespective of PD-L1 Expression

End point title	Percentage of Participants With DC as Assessed by Investigator Irrespective of PD-L1 Expression

End point description:

DC was defined as a best overall response of CR, PR, non-CR/non-PD or SD according to RECIST v1.1 as assessed by investigator. CR was defined as complete disappearance of all target and non-target lesions, with the exception of nodal disease and sustained for at least 4 weeks. All lymph nodes must decrease to normal size (short axis<10mm). PR was defined as at least 30% decrease in the sum of the longest dimensions of target lesions taking as reference the baseline sum longest dimensions. Non-CR/Non-PD was defined as persistence of any non-target lesions and/or tumor marker level above the normal limits. SD was defined as not to qualify for CR, PR or PD for target lesions and followed PR only if the sum increased by less than 20% from the nadir (smallest sum of diameters consider baseline and all assessments prior to the time point under evaluation), but enough that a previously documented 30% decrease no longer holds. FAS included all randomized participants.

End point type	Secondary

End point timeframe:

From date of randomization until PD (maximum up to approximately 89 months)

End point values	Avelumab + Axitinib	Sunitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	442	444		
Units: Percentage of participants				
number (confidence interval 95%)	85.1 (81.4 to 88.3)	76.4 (72.1 to 80.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Disease Control (DC) as Assessed by BICR Irrespective of PD-L1 Expression

End point title	Percentage of Participants With Disease Control (DC) as Assessed by BICR Irrespective of PD-L1 Expression

End point description:

DC was defined as a best overall response of CR, PR, non-CR/non-PD or stable disease (SD) according

to RECIST v1.1 as assessed by BICR. CR was defined as complete disappearance of all target and non-target lesions, with the exception of nodal disease and sustained for at least 4 weeks. All lymph nodes must decrease to normal size (short axis<10mm). PR was defined as at least 30% decrease in the sum of the longest dimensions of target lesions taking as reference the baseline sum longest dimensions. Non-CR/Non-PD was defined as persistence of any non-target lesions and/or tumor marker level above the normal limits. SD was defined as not to qualify for CR, PR or PD for target lesions and followed PR only if the sum increased by less than 20% from the nadir (smallest sum of diameters consider baseline and all assessments prior to the time point under evaluation), but enough that a previously documented 30% decrease no longer holds. FAS included all randomized participants.

End point type	Secondary

End point timeframe:

From date of randomization until PD (maximum up to approximately 26 months)

End point values	Avelumab + Axitinib	Sunitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	442	444		
Units: Percentage of participants				
number (confidence interval 95%)	82.8 (79.0 to 86.2)	73.4 (69.1 to 77.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: TTR as Assessed by Investigator in Participants Irrespective of PD-L1 Expression

End point title	TTR as Assessed by Investigator in Participants Irrespective of PD-L1 Expression

End point description:

TTR was defined as the time from randomization to the first documentation of objective tumor response according to RECIST v1.1 as assessed by investigator (CR or PR) which is subsequently confirmed. CR was defined as complete disappearance of all target and non-target lesions with the exception of nodal disease. All lymph nodes must decrease to normal size (short axis<10 mm). All target lesions must be assessed. PR was defined as greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. All target lesions must be assessed. FAS included all randomized participants. Here "Participants Analyzed" signifies number of participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From the date of randomization to the first documentation of objective response (CR or PR) (maximum up to approximately 89 months)

End point values	Avelumab + Axitinib	Sunitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	264	142		
Units: Months				
median (full range (min-max))	2.8 (1.1 to 34.5)	2.8 (1.2 to 65.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Tumor Response (TTR) as Assessed by BICR in Participants Irrespective of PD-L1 Expression

End point title	Time to Tumor Response (TTR) as Assessed by BICR in Participants Irrespective of PD-L1 Expression

End point description:

TTR was defined as the time from randomization to the first documentation of objective tumor response according to RECIST v1.1 as assessed by BICR (CR or PR) which is subsequently confirmed. CR was defined as complete disappearance of all target and non-target lesions with the exception of nodal disease. All lymph nodes must decrease to normal size (short axis<10 mm). All target lesions must be assessed. PR was defined as greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. All target lesions must be assessed. FAS included all randomized participants. Here "Participants Analyzed" signifies number of participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From the date of randomization to the first documentation of objective response (CR or PR) (maximum up to approximately 26 months)

End point values	Avelumab + Axitinib	Sunitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	227	114		
Units: Months				
median (full range (min-max))	2.6 (1.2 to 13.8)	3.2 (1.2 to 11.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: PFS as Assessed by Investigator in Participants Irrespective of PD-L1 Expression

End point title	PFS as Assessed by Investigator in Participants Irrespective of PD-L1 Expression

End point description:

Investigator assessed PFS: time from the date of randomization to the date of the first documentation of PD according to RECIST v1.1 or death due to any cause, whichever occurred first. PFS data was

censored on date of last adequate tumor assessment for participants who did not have an event (PD or death), who started new anti-cancer therapy prior to an event or for participants with an event after 2 or more missing tumor assessments. PD was defined as at least a 20% increase in the sum of all the longest diameter of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to relative increase of 20 %, sum must have also demonstrated an absolute > of at least 5 mm. The appearance of one or more new lesions was also considered progression. FAS included all randomized participants.

End point type	Secondary

End point timeframe:

From date of randomization until PD or death due to any cause or censoring date, whichever occurred first (maximum up to approximately 89 months)

End point values	Avelumab + Axitinib	Sunitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	442	444		
Units: Months				
median (confidence interval 95%)	13.9 (11.1 to 16.6)	8.5 (8.2 to 9.7)		

Statistical analyses

Statistical analysis title	Avelumab + Axitinib Versus Sunitinib
Comparison groups	Avelumab + Axitinib v Sunitinib
Number of subjects included in analysis	886
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	< 0.0001 [10]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.565
upper limit	0.768

Notes:

[9] - 2-sided p-value

[10] - 2-sided p-value

Secondary: DR as Assessed by Investigator in Participants Irrespective of PD-L1 Expression

End point title	DR as Assessed by Investigator in Participants Irrespective of PD-L1 Expression

End point description:

Investigator assessed DR: time from first documentation of OR (confirmed CR or PR) to date of first documentation of objective tumor progression (PD) assessed by investigator or death due to any cause whichever occurred first. As per RECIST v1.1. CR: complete disappearance of all target and non-target lesions with the exception of nodal disease. All lymph nodes must decrease to normal size (short axis<10 mm). All target lesions must be assessed. PR: >=30% decrease under baseline of the sum of diameters of all target measurable lesions. All target lesions must be assessed. PD: at least a 20%

increase in the sum of all the longest diameter of target lesions, taking as reference the smallest sum on study. In addition to relative increase of 20%, sum must have also demonstrated an absolute > of at least 5 mm. Appearance of one or more new lesions was also considered progression. FAS was used. N= participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From documentation of OR until date of first documentation of PD or death due to any cause, whichever occurred first (maximum up to approximately 89 months)

End point values	Avelumab + Axitinib	Sunitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	264	142		
Units: Months				
median (confidence interval 95%)	19.4 (16.4 to 22.3)	14.5 (8.7 to 16.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DR) as Assessed by BICR in Participants Irrespective of PD-L1 Expression

End point title	Duration of Response (DR) as Assessed by BICR in Participants Irrespective of PD-L1 Expression

End point description:

BICR assessed DR: time from first documentation of OR(confirmed CR or PR) to date of first documentation of objective tumor progression assessed by BICR or death due to any cause whichever occurred first. As per RECIST v1.1. CR: complete disappearance of all target and non-target lesions with the exception of nodal disease. All lymph nodes must decrease to normal size (short axis<10 mm). All target lesions must be assessed. PR: >=30% decrease under baseline of sum of diameters of all target measurable lesions. All target lesions must be assessed. PD: at least 20% increase in sum of all longest diameter of target lesions, taking as reference smallest sum on study. In addition to relative increase of 20%, sum must have also demonstrated an absolute > of at least 5 mm. Appearance of one or more new lesions was also considered progression. FAS was used. N= participants evaluable for this endpoint. "99999" = values could not estimated due to insufficient number of participants with event.

End point type	Secondary

End point timeframe:

From documentation of OR until date of first documentation of PD or death due to any cause, whichever occurred first (maximum up to approximately 26 months)

End point values	Avelumab + Axitinib	Sunitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	227	114		
Units: Months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (11.2 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-Emergent Adverse Events (AEs) Graded Based on National Cancer Institute -Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version (V) 4.03

End point title	Number of Participants With Treatment-Emergent Adverse Events (AEs) Graded Based on National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version (V) 4.03

End point description:

An AE was any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. TEAEs were those events with onset dates occurring during the on-treatment period for the first time, or if the worsening of an event was during the on-treatment period (time from the first dose of study treatment through 90 days after last dose of study treatment or start day of new anti-cancer drug therapy–1 day). As per NCI-CTCAE v4.03, grade 1=mild, grade 2=moderate, grade 3=severe, grade 4=life-threatening consequences and grade 5=death. Safety analysis set included all participants who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

From start of study treatment until 90 days after last dose of study treatment (maximum up to approximately 92 months)

End point values	Avelumab + Axitinib	Sunitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	434	439		
Units: Participants				
Grade 1	5	17		
Grade 2	64	73		
Grade 3	271	268		
Grade 4	64	54		
Grade 5	30	24		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival on Next-line Therapy (PFS2) in Participants Irrespective of PD-L1 Expression

End point title	Progression-Free Survival on Next-line Therapy (PFS2) in Participants Irrespective of PD-L1 Expression

End point description:

PFS2 is defined as the time (in months) from randomization to discontinuation of next-line treatment after first objective disease progression by investigator assessment, second objective disease progression by investigator assessment after initiation of next-line treatment, or death from any cause, whichever occurred first. PD was defined as at least a 20% increase in the sum of all the longest diameter of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to relative increase of 20 %, sum must have also demonstrated an absolute > of at least 5 mm. The appearance of one or more new lesions was also considered progression. FAS included all randomized participants.

End point type	Secondary

End point timeframe:

From date of randomization until PD or death due to any cause or censoring date, whichever occurred first (maximum up to approximately 89 months)

End point values	Avelumab + Axitinib	Sunitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	442	444		
Units: Months				
median (confidence interval 95%)	30.4 (25.8 to 34.6)	19.4 (17.0 to 22.4)		

Statistical analyses

Statistical analysis title	Avelumab + Axitinib Versus Sunitinib
Comparison groups	Avelumab + Axitinib v Sunitinib
Number of subjects included in analysis	886
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.551
upper limit	0.754

Secondary: Number of Participants According to Grade Shift in Hematology Parameters

End point title	Number of Participants According to Grade Shift in Hematology Parameters

End point description:

Following hematology parameters were assessed: hemoglobin decreased (anemia), hemoglobin increased, lymphocyte count decreased, lymphocyte count increased, neutrophil count decreased, platelet count decreased and white blood cell (WBC) decreased. Laboratory abnormalities were graded as per NCI- CTCAE v 4.03 where, grade(G) 0= non-missing lab value that does not meet either of G1 through 4 criteria, G1=mild, G2=moderate, G3=severe, G4=life-threatening consequences and G5=death. Baseline was defined as last assessment prior to first dose of study treatment. Number of participants with a baseline grade of either 0,1,2,3 or 4 which shifted to G3-4 post-baseline are reported

in this endpoint. Only non-zero categories for any reporting arm are reported. Safety analysis set included all participants who received at least one dose of study drug. N= number of participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From start of study treatment until 90 days after last dose of study treatment (maximum up to approximately 92 months)

End point values	Avelumab + Axitinib	Sunitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	434		
Units: Participants				
Anemia (B G0 to PB G3-4)	3	9		
Anemia (B G1 to PB G3-4)	6	21		
Anemia (B G2 to PB G3-4)	4	14		
Anemia (B G3 to PB G3-4)	0	2		
Lymphocytes count decreased (B G0 to PB G3-4)	21	53		
Lymphocytes count decreased (B G1 to PB G3-4)	11	18		
Lymphocytes count decreased (B G2 to PB G3-4)	7	15		
Lymphocytes count decreased (B G3 to PB G3-4)	2	6		
Neutrophils count decreased (B G0 to PB G3-4)	7	108		
Neutrophils count decreased (B G1 to PB G3-4)	0	2		
Neutrophils count decreased (B G2 to PB G3-4)	0	1		
Platelets count decreased (B G0 to PB G3-4)	3	61		
Platelets count decreased (B G1 to PB G3-4)	1	6		
WBC decreased (B G0 to PB G3-4)	1	35		
WBC decreased (B G1 to PB G3-4)	0	7		
WBC decreased (B G2 to PB G3-4)	0	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants According to Grade Shift in Chemistry Parameters

End point title	Number of Participants According to Grade Shift in Chemistry Parameters

End point description:

Following chemistry parameters were assessed: alanine aminotransferase(ALT) increased,alkaline phosphatase(ALP) increased, aspartate aminotransferase(AST) increased (inc.), blood bilirubin increased, cholesterol high, creatinine phosphokinase(CPK) increased, creatinine increased,gamma glutamyl transferase(GGT) increased, hypercalcemia, hyperglycemia, hyperkalemia, hypermagnesmia,

hypernatremia, hypertriglyceridemia, hypoalbuminemia, hypokalemia, hypomagnesemia, hyponatremia, lipase increased and serum amylase increased. Laboratory abnormality graded- NCI CTCAE v4.03; G0=non-missing lab value that does not meet either of G1 through 4 criteria, G1=mild,G2=moderate,G3=severe,G4=life-threatening consequences,G5=death. No. of participants with B grade of either 0,1,2,3/4 which shifted to G3-4 PB are reported. Only non-zero categories for any reporting arm reported. Safety analysis set. N= no. of participants evaluable for this endpoint. n= no. of participants evaluable for specified rows.

End point type	Secondary

End point timeframe:

From start of study treatment until 90 days after last dose of study treatment (maximum up to approximately 92 months)

End point values	Avelumab + Axitinib	Sunitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	433		
Units: Participants				
ALT increased (B G0 to PB G3-4) (n=428,433)	42	19		
ALT increased (B G1 to PB G3-4) (n=428,433)	3	0		
ALP increased (B G0 to PB G3-4) (n=428,433)	9	0		
ALP increased (B G1 to PB G3-4) (n=428,433)	5	6		
ALP increased (B G2 to PB G3-4) (n=428,433)	1	3		
ALP increased (B G3 to PB G3-4) (n=428,433)	4	1		
AST increased (B G0 to PB G3-4) (n=428,433)	26	16		
AST increased (B G1 to PB G3-4) (n=428,433)	6	4		
AST increased (B G3 to PB G3-4) (n=428,433)	1	0		
Blood bilirubin inc(B G0 to PB G3-4) (n=428,433)	3	6		
Blood bilirubin inc(B G1 to PB G3-4) (n=428,433)	2	0		
Cholesterol high (B G0 to PB G3-4) (n=419,413)	8	3		
Cholesterol high (B G1 to PB G3-4) (n=419,413)	4	3		
Cholesterol high (B G2 to PB G3-4) (n=419,413)	0	1		
CPK increased (B G0 to PB G3-4) (n=417,415)	7	7		
CPK increased (B G1 to PB G3-4) (n=417,415)	0	2		
CPK increased (B G2 to PB G3-4) (n=417,415)	0	1		
CPK increased (B G3 to PB G3-4) (n=417,415)	1	0		
Creatinine increased(B G0 to PB G3-4) (n=428,433)	7	2		
Creatinine increased(B G1 to PB G3-4) (n=428,433)	4	5		

Creatinine increased(B G2 to PB G3-4) (n=428,433)	0	1		
Creatinine increased(B G3 to PB G3-4) (n=428,433)	0	1		
GGT increased (B G0 to PB G3-4) (n=419,415)	15	16		
GGT increased (B G1 to PB G3-4) (n=419,415)	20	7		
GGT increased (B G2 to PB G3-4) (n=419,415)	12	4		
GGT increased (B G3 to PB G3-4) (n=419,415)	7	2		
GGT increased (B G4 to PB G3-4) (n=419,415)	0	1		
Hypercalcemia (B G0 to PB G3-4) (n=418,419)	4	4		
Hypercalcemia (B G1 to PB G3-4) (n=418,419)	1	2		
Hypercalcemia (B G2 to PB G3-4) (n=418,419)	1	1		
Hypercalcemia (B G3 to PB G3-4) (n=418,419)	0	2		
Hypercalcemia (B G4 to PB G3-4) (n=418,419)	0	1		
Hyperglycemia (B G0 to PB G3-4) (n=428,433)	37	20		
Hyperglycemia (B G1 to PB G3-4) (n=428,433)	4	3		
Hyperglycemia (B G2 to PB G3-4) (n=428,433)	5	3		
Hyperglycemia (B G3 to PB G3-4) (n=428,433)	6	4		
Hyperkalemia (B G0 to PB G3-4) (n=428,433)	19	16		
Hyperkalemia (B G1 to PB G3-4) (n=428,433)	1	5		
Hyperkalemia (B G2 to PB G3-4) (n=428,433)	3	3		
Hyperkalemia (B G3 to PB G3-4) (n=428,433)	1	0		
Hyperkalemia (B G4 to PB G3-4) (n=428,433)	0	1		
Hypermagnesemia (B G0 to PB G3-4) (n=428,433)	13	20		
Hypermagnesemia (B G1 to PB G3-4) (n=428,433)	1	2		
Hypernatremia (B G0 to PB G3-4) (n=428,433)	7	2		
Hypertriglyceridemia(B G0 to PB G3-4) (n=419,411)	18	3		
Hypertriglyceridemia(B G1 to PB G3-4) (n=419,411)	31	23		
Hypertriglyceridemia(B G2 to PB G3-4) (n=419,411)	15	6		
Hypertriglyceridemia(B G3 to PB G3-4) (n=419,411)	4	5		
Hypertriglyceridemia(B G4 to PB G3-4) (n=419,411)	0	1		
Hypoalbunemia (B G0 to PB G3-4) (n=418,419)	3	6		
Hypoalbunemia (B G1 to PB G3-4) (n=418,419)	1	1		

Hypoalbunemia (B G2 to PB G3-4) (n=418,419)	2	2		
Hypoalbunemia (B G3 to PB G3-4) (n=418,419)	1	2		
Hypocalcemia (B G0 to PB G3-4) (n=418,419)	4	4		
Hypocalcemia (B G1 to PB G3-4) (n=418,419)	0	1		
Hypocalcemia (B G2 to PB G3-4) (n=418,419)	1	0		
Hypoglycemia (B G0 to PB G3-4) (n=428,433)	2	1		
Hypokalemia (B G0 to PB G3-4) (n=428,433)	17	15		
Hypomagnesemia (B G0 to PB G3-4) (n=428,433)	3	1		
Hypokalemia (B G2 to PB G3-4) (n=428,433)	2	1		
Hypomagnesemia (B G1 to PB G3-4) (n=428,433)	2	1		
Hypomagnesemia (B G2 to PB G3-4) (n=428,433)	1	0		
Hyponatremia (B G0 to PB G3-4) (n=428,433)	42	35		
Hyponatremia (B G1 to PB G3-4) (n=428,433)	19	14		
Hyponatremia (B G3 to PB G3-4) (n=428,433)	1	2		
Lipase increased (B G0 to PB G3-4) (n=419,414)	63	27		
Lipase increased (B G1 to PB G3-4) (n=419,414)	19	8		
Lipase increased (B G2 to PB G3-4) (n=419,414)	7	3		
Lipase increased (B G3 to PB G3-4) (n=419,414)	2	7		
Lipase increased (B G4 to PB G3-4) (n=419,414)	1	0		
Serum amylase inc(B G0 to PB G3-4) (n=412,407)	21	4		
Serum amylase inc(B G1 to PB G3-4) (n=412,407)	12	4		
Serum amylase inc(B G2 to PB G3-4) (n=412,407)	4	4		
Serum amylase inc(B G3 to PB G3-4) (n=412,407)	1	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Vital Signs - Blood Pressure at Day 1 of Cycle 2, 3, 4, 5, 6, 7 and End of Treatment (EOT) Visit

End point title	Change From Baseline in Vital Signs - Blood Pressure at Day 1 of Cycle 2, 3, 4, 5, 6, 7 and End of Treatment (EOT) Visit

End point description:

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured with the participant in the seated position after the participant had been sitting quietly for at least 5 minutes. Safety analysis

set included all participants who received at least one dose of study drug. "n" signifies number of participants evaluable for the specified time points.

End point type	Secondary

End point timeframe:

Baseline (pre-dose on Day 1 of Cycle 1), Day 1 of Cycle 2, 3, 4, 5, 6, 7, EOT visit (maximum up to approximately 89 months) (each cycle=42 days)

End point values	Avelumab + Axitinib	Sunitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	434	439		
Units: Millimeters of mercury				
arithmetic mean (standard deviation)				
Baseline: Sitting SBP (n=434,439)	126.5 (± 13.52)	126.3 (± 12.00)		
Change at Cycle 2, Day 1: Sitting SBP(n=380,344)	4.7 (± 16.08)	0.8 (± 12.49)		
Change at Cycle 3, Day 1: Sitting SBP(n=363,310)	3.8 (± 16.43)	1.2 (± 12.81)		
Change at Cycle 4, Day 1: Sitting SBP(n=342,271)	3.0 (± 15.95)	0.1 (± 13.01)		
Change at Cycle 5, Day 1: Sitting SBP(n=332,244)	2.5 (± 15.42)	-0.1 (± 12.26)		
Change at Cycle 6, Day 1: Sitting SBP(n=310,215)	1.6 (± 15.39)	-0.1 (± 12.97)		
Change at Cycle 7, Day 1: Sitting SBP(n=282,191)	1.9 (± 15.39)	0.4 (± 13.56)		
Change at End of Treatment:SittingSBP (n=205,273)	0.9 (± 17.40)	1.7 (± 15.67)		
Baseline: Sitting DBP (n=434,439)	75.7 (± 9.32)	75.9 (± 9.41)		
Change at Cycle 2, Day 1: Sitting DBP(n=380,344)	5.8 (± 10.92)	-0.1 (± 8.60)		
Change at Cycle 3, Day 1: Sitting DBP(n=363,310)	4.9 (± 10.98)	0.0 (± 9.64)		
Change at Cycle 4, Day 1: Sitting DBP(n=342,271)	4.8 (± 11.61)	-1.9 (± 9.30)		
Change at Cycle 5, Day 1: Sitting DBP(n=332,244)	4.5 (± 11.17)	-1.9 (± 9.71)		
Change at Cycle 6, Day 1: Sitting DBP(n=310,215)	3.8 (± 10.18)	-1.3 (± 9.89)		
Change at Cycle 7, Day 1: Sitting DBP(n=282,191)	3.8 (± 11.04)	-1.1 (± 9.90)		
Change at End of Treatment:SittingDBP (n=205,273)	1.5 (± 12.70)	-0.9 (± 10.92)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Vital Signs - Pulse Rate at Day 1 of Cycle 2, 3, 4, 5, 6, 7 and EOT Visit

End point title	Change From Baseline in Vital Signs - Pulse Rate at Day 1 of Cycle 2, 3, 4, 5, 6, 7 and EOT Visit

End point description:

Pulse rate (PR) was measured with the participant in the seated position after the participant had been sitting quietly for at least 5 minutes. Safety analysis set included all participants who received at least one dose of study drug. Here "Participants Analyzed" signifies number of participants evaluable for this outcome measure. "n" signifies number of participants evaluable for the specified time points.

End point type	Secondary

End point timeframe:

Baseline (pre-dose on Day 1 of Cycle 1), Day 1 of Cycle 2, 3, 4, 5, 6, 7, EOT visit (maximum up to approximately 89 months) (each cycle=42 days)

End point values	Avelumab + Axitinib	Sunitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	433	439		
Units: Beats per minute				
arithmetic mean (standard deviation)				
Baseline: Sitting PR (n=433,439)	75.4 (± 12.49)	75.6 (± 12.63)		
Change at Cycle 2, Day 1: Sitting PR (n=347,319)	0.4 (± 12.77)	3.1 (± 10.69)		
Change at Cycle 3, Day 1: Sitting PR(n=338,289)	0.8 (± 12.58)	3.1 (± 11.34)		
Change at Cycle 4, Day 1: Sitting PR(n=327,244)	-0.6 (± 12.79)	2.8 (± 10.34)		
Change at Cycle 5, Day 1: Sitting PR(n=319,227)	-0.5 (± 12.00)	2.5 (± 10.82)		
Change at Cycle 6, Day 1: Sitting PR(n=299,203)	-1.9 (± 12.37)	1.6 (± 10.75)		
Change at Cycle 7, Day 1: Sitting PR(n=269,182)	-1.9 (± 11.69)	2.1 (± 10.13)		
Change at End of Treatment:Sitting PR (n=196,250)	2.9 (± 15.29)	3.5 (± 12.27)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants who Discontinued Treatment due to Toxicity

End point title	Number of Participants who Discontinued Treatment due to Toxicity

End point description:

Number of participants who discontinued treatment due to toxicity are reported in this endpoint. Safety analysis set included all participants who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

From first dose of study treatment until discontinuation of study treatment (maximum up to approximately 92 months)

End point values	Avelumab + Axitinib	Sunitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	434	439		
Units: Participants	136	65		

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Plasma Concentration (Ctrough) of Avelumab

End point title	Trough Plasma Concentration (Ctrough) of Avelumab[11]

End point description:

Predose concentration during multiple dosing. Avelumab PK concentration analysis set: all participants who had at least one post-dose concentration above lower limit of quantitation (LLQ) for avelumab. Here "Participants Analyzed" signifies participants evaluable for this endpoint. "n" signifies number of participants evaluable for the specified rows. This endpoint was not planned to be analyzed in ‘’Sunitinib’’ reporting group.

End point type	Secondary

End point timeframe:

Pre dose (0 hour) on Day 1, 15 and 29 of Cycle 1, Day 1 and 29 of Cycles 2, 3, 4 and Day 1 of Cycle 6

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint is specific to Avelumab; hence, only arm for Avelumab was included.

End point values	Avelumab + Axitinib			
Subject group type	Reporting group			
Number of subjects analysed	389			
Units: Micrograms per milliliter				
geometric mean (geometric coefficient of variation)				
Cycle 1 (day 1) (n=389)	4.218 (± 1232)			
Cycle 1 (day 15) (n=267)	18.69 (± 102)			
Cycle 1 (day 29) (n=270)	21.99 (± 96)			
Cycle 2 (day 1) (n=314)	24.87 (± 92)			
Cycle 2 (day 29) (n=215)	22.62 (± 113)			
Cycle 3 (day 1) (n=202)	26.04 (± 98)			
Cycle 3 (day 29) (n=181)	30.13 (± 82)			
Cycle 4 (day 1) (n=186)	29.15 (± 98)			
Cycle 4 (day 29) (n=160)	31.38 (± 86)			
Cycle 6 (day 1) (n=130)	39.11 (± 58)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Treatment Discontinuation/Failure Due to Toxicity

End point title	Time to Treatment Discontinuation/Failure Due to Toxicity

End point description:

Time to treatment discontinuation/ failure due to toxicity was defined as the time from first dose of study treatment to discontinuation of study treatment due to an adverse event or death due to study treatment toxicity. Safety analysis set included all participants who received at least one dose of study drug. Here "Participants Analyzed" signifies number of participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From first dose of study treatment until discontinuation of study treatment (maximum up to approximately 92 months)

End point values	Avelumab + Axitinib	Sunitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	65		
Units: Months				
arithmetic mean (standard deviation)	13.5 (± 17.41)	10.5 (± 12.82)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Plasma Concentration (Cmax) of Axitinib

End point title	Maximum Plasma Concentration (Cmax) of Axitinib[12]

End point description:

Axitinib PK concentration analysis set: all participants who received at least one dose of study drug and had at least one post-dose concentration above LLQ for axitinib. Here "Participants Analyzed" signifies participants evaluable for this endpoint. "n" signifies number of participants evaluable for the specified rows. This endpoint was not planned to be analyzed in ‘‘Sunitinib’’ reporting group.

End point type	Secondary

End point timeframe:

2 hours post-dose on Day 1, pre-dose and 2 hours post dose on Days 15 and 29 of Cycle 1

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint is specific to Axitinib; hence, only arm for Axitinib was included.

End point values	Avelumab + Axitinib			
Subject group type	Reporting group			
Number of subjects analysed	316			
Units: Nanograms per milliliter				
geometric mean (geometric coefficient of variation)				
Cycle1 (day 1); Post Dose (n=316)	17.93 (± 182)			
Cycle1 (day 15); Pre-Dose (n=312)	4.904 (± 172)			
Cycle1 (day 15); Post Dose (n=286)	18.45 (± 157)			
Cycle1 (day 29); Pre-Dose (n=302)	6.272 (± 174)			

Cycle1 (day 29); Post Dose (n=272)	17.19 (± 174)			

Statistical analyses

No statistical analyses for this end point

Secondary: Ctrough of Axitinib

End point title	Ctrough of Axitinib[13]

End point description:

Predose concentration during multiple dosing. Axitinib PK concentration analysis set: all participants who received at least one dose of study drug and had at least one post-dose concentration above lower limit of quantitation (LLQ) for axitinib. Here "Number of Participants Analyzed" signifies participants evaluable for this endpoint. "Number Analyzed" signifies number of participants evaluable for the specified rows. This endpoint was not planned to be analyzed in ‘’Sunitinib’’ reporting group.

End point type	Secondary

End point timeframe:

Pre dose (0 hour) on day 15 and 29 of cycle 1

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint is specific to Axitinib; hence, only arm for Axitinib was included.

End point values	Avelumab + Axitinib			
Subject group type	Reporting group			
Number of subjects analysed	312			
Units: Nanograms per milliliter				
geometric mean (geometric coefficient of variation)				
Cycle1 (day 15) (n=312)	4.904 (± 172)			
Cycle1 (day 29) (n=302)	6.272 (± 174)			

Statistical analyses

No statistical analyses for this end point

Secondary: PFS in PD-L1 Biomarker-Positive and PD-L1 Biomarker-Negative Subgroups

End point title	PFS in PD-L1 Biomarker-Positive and PD-L1 Biomarker-Negative Subgroups

End point description:

PFS: time from date of randomization to date of first documentation of PD according to RECIST v1.1 or death due to any cause, whichever occurred first. PFS data was censored on date of last adequate tumor assessment for participants who did not have an event (PD or death), who started new anti-cancer therapy prior to an event or for participants with an event after 2 or more missing tumor assessments. PD was defined as at least 20% increase in sum of all longest diameter of target lesions, taking as reference smallest sum on study. In addition to relative increase of 20 %, sum must have also demonstrated an absolute > of at least 5 mm. Biomarker positive/negative subset in FAS included

participants who had at least one biomarker baseline assessment. “N”= participants evaluable for this endpoint. "n" number of participants evaluable for specified rows. “99999” = upper limit of 95% CI was not estimable due to insufficient number of participants with event.

End point type	Secondary

End point timeframe:

From date of randomization to the first documentation of PD or death due to any cause or censoring date, whichever occurred first (maximum up to approximately 26 months)

End point values	Avelumab + Axitinib	Sunitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	402	410		
Units: Months				
median (confidence interval 95%)				
PD-L1 Positive Tumors (n=270,290)	13.8 (11.1 to 99999)	7.2 (5.7 to 9.7)		
PD-L1 Negative Tumors (n=132,120)	16.1 (9.7 to 99999)	11.1 (6.9 to 17.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With OR in PD-L1 Biomarker-Positive and PD-L1 Biomarker-Negative Subgroups

End point title	Percentage of Participants With OR in PD-L1 Biomarker-Positive and PD-L1 Biomarker-Negative Subgroups

End point description:

OR was defined as best overall response of CR or PR according to RECIST v1.1 as assessed by BICR recorded from date of randomization until disease progression. CR was defined as complete disappearance of all target and non-target lesions with the exception of nodal disease. All lymph nodes must decrease to normal size (short axis<10 mm). All target lesions must be assessed. PR was defined as greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. All target lesions must be assessed. Biomarker positive/negative subset in FAS included participants who had at least one biomarker baseline assessment. Here "Participants Analyzed" signifies participants evaluable for this endpoint. "n" signifies number of participants evaluable for the specified rows.

End point type	Secondary

End point timeframe:

From date of randomization until PD (maximum up to approximately 26 months)

End point values	Avelumab + Axitinib	Sunitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	402	410		
Units: Percentage of participants				
number (confidence interval 95%)				
PD-L1 Positive Tumors (n=270,290)	55.2 (49.0 to 61.2)	25.5 (20.6 to 30.9)		

PD-L1 Negative Tumors (n=132,120)	47.0 (38.2 to 55.8)	28.3 (20.5 to 37.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Positive PD-L1 Biomarker Expression in Pre-treatment Tumor Tissue

End point title	Number of Participants With Positive PD-L1 Biomarker Expression in Pre-treatment Tumor Tissue

End point description:

Tumor biospecimens from pre-treatment tissue samples were analyzed by immunohistochemistry for PD-L1 biomarker expression. Number of participants with positive PD-L1 biomarker expression are reported in this endpoint. Biomarker analysis set for biomarkers that are measured only at screening, included all participants who received at least one dose of study drug and who had at least one screening biomarker assessment. Here "n" signifies participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

At screening

End point values	Avelumab + Axitinib	Sunitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	397	407		
Units: Participants	266	288		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With DC in Biomarker-Positive Subgroup

End point title	Percentage of Participants With DC in Biomarker-Positive Subgroup

End point description:

DC was defined as a best overall response of CR, PR, or SD according to the RECIST v.1.1 recorded from randomization until disease progression or death due to any cause, whichever occurred first. CR was defined as complete disappearance of all target and non-target lesions with the exception of nodal disease. All lymph nodes must decrease to normal size (short axis<10 mm). All target lesions must be assessed. PR was defined as greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. All target lesions must be assessed. SD was defined as PR that the sum increases by less than 20% from the nadir, (smallest sum of diameters consider baseline and all assessments prior to the time point under evaluation), but enough that a previously documented 30% decrease no longer holds. Biomarker positive subset in FAS included participants who had at least one biomarker baseline assessment.

End point type	Secondary

End point timeframe:

From date of randomization until PD or death, whichever occurred first (maximum up to approximately 26 months)

End point values	Avelumab + Axitinib	Sunitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	270	290		
Units: Percentage of participants				
number (confidence interval 95%)	84.4 (79.6 to 88.6)	71.0 (65.4 to 76.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: TTR in Biomarker-Positive Subgroup

End point title	TTR in Biomarker-Positive Subgroup

End point description:

TTR was defined as the time from randomization to the first documentation of objective tumor response (CR or PR) according to RECIST v1.1 which is subsequently confirmed. CR was defined as complete disappearance of all target and non-target lesions with the exception of nodal disease. All lymph nodes must decrease to normal size (short axis<10 mm). All target lesions must be assessed. PR was defined as greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. All target lesions must be assessed. Biomarker positive subset in FAS included participants who had at least one biomarker baseline assessment. Here "Participants Analyzed" signifies participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From the date of randomization to the first documentation of objective response (CR or PR) (maximum up to approximately 26 months)

End point values	Avelumab + Axitinib	Sunitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	74		
Units: Months				
median (full range (min-max))	1.6 (1.2 to 10.1)	3.0 (1.2 to 11.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: DR in PD-L1 Biomarker-Positive and PD-L1 Biomarker-Negative

Subgroups

End point title	DR in PD-L1 Biomarker-Positive and PD-L1 Biomarker-Negative Subgroups

End point description:

DR: time from first documentation of OR (confirmed CR or PR) to date of first documentation of PD or death due to any cause, whichever occurred first. As per RECIST version 1.1, CR: disappearance of all target and non-target lesions, and sustained for at least 4 weeks. Any pathological lymph nodes (target or non-target) must have reduction in short axis to <10 mm. PR: at least 30%< in sum of longest dimensions of target lesions taking as reference baseline sum longest dimensions. PD: defined as at least a 20% > in sum of diameters of target lesions, taking as reference the smallest sum on study. In addition to relative increase of 20%, sum must have also demonstrated an absolute increase of at least 5 mm. Biomarker positive/negative subset in FAS used. "N" = participants evaluable for this endpoint. "n" signifies number of participants evaluable for specified rows. “99999” = values were not estimable due to insufficient number of participants with event.

End point type	Secondary

End point timeframe:

From documentation of OR until date of first documentation of PD or death due to any cause, whichever occurred first (maximum up to approximately 26 months)

End point values	Avelumab + Axitinib	Sunitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	211	108		
Units: Months				
median (confidence interval 95%)				
PD-L1 Positive Tumors (n=149,74)	99999 (99999 to 99999)	99999 (10.9 to 99999)		
PD-L1 Negative Tumors (n=62,34)	99999 (11.1 to 99999)	99999 (9.0 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Symptom Deterioration (TTD) for Functional Assessment of Cancer Therapy (FACT)-Kidney Symptom Index - Disease Related Symptoms (FKSI-DRS)

End point title	Time to Symptom Deterioration (TTD) for Functional Assessment of Cancer Therapy (FACT)-Kidney Symptom Index - Disease Related Symptoms (FKSI-DRS)

End point description:

TTD was defined as the time from date of randomization to the first time the participant’s score showed a 3-point or greater decrease in FKSI-DRS. FKSI was used to assess symptoms and quality of life (QoL) for those diagnosed with advanced kidney cancer and it consisted of 19 questions. A 9-item subscale of the FKSI known as FKSI-Disease Related Symptoms subscale (FKSI-DRS). This subscale included 9 items: lack of energy, pain, losing weight, bone pain, fatigue, shortness of breath, coughing, bothered by fevers, and hematuria. Each of the 9 items was answered on a 5-point Likert-type scale ranging from 0 to 4 (0= not at all, 1= a little bit, 2= somewhat, 3= quite a bit, 4= very much). Total FKSI-DRS score = sum of the 9 item scores; total range: 0 - 36; 0 (no symptoms) to 36 (very much); higher score indicated greater presence of symptoms. FAS included all randomized participants.

End point type	Secondary

End point timeframe:

Date of randomization to the first time the participant’s score showed a 3-point or greater decrease in

End point values	Avelumab + Axitinib	Sunitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	442	444		
Units: Months				
median (full range (min-max))	4.2 (4.2 to 5.7)	6.3 (5.5 to 8.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Quality of Life (EuroQol) 5-Dimension 5 Levels (EQ-5D-5L) Utility Score

End point title	Change From Baseline in European Quality of Life (EuroQol) 5-Dimension 5 Levels (EQ-5D-5L) Utility Score

End point description:

EQ-5D-5L is 5-item participant-completed questionnaire designed to assess health status in terms of a single utility score. EQ-5D health state profile is comprised of 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: 1=no problems, 2=slight problems, 3=moderate problems, 4=severe problems, and 5=extreme problems. Overall scores ranged from 0 to 1, with low scores representing higher level of dysfunction. Published UK weights were used to create single summary utility score. Utility scores range from -0.594 to 1, with higher scores=health status. FAS included all randomized participants. All participants reported under "N" contributed data to table; however, may not have evaluable data for every row. "n" signifies number of participants evaluable for specified rows. "99999"= SD could not be calculated as only 1 participant was analyzed. “88888” mean and SD could not be calculated as 0 participant was analyzed.

End point type	Secondary

End point timeframe:

Baseline, Day 1 of Cycle 2 to Cycle 60, End of treatment (any Day from Day 1 of dosing; maximum up to approximately 89 months)

End point values	Avelumab + Axitinib	Sunitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	442	444		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Cycle 2 (Day 1) (n=381,355)	-0.034 (± 0.1743)	0.001 (± 0.1632)		
Cycle 3 (Day 1) (n=356,317)	-0.023 (± 0.1826)	-0.017 (± 0.1804)		
Cycle 4 (Day 1) (n=335,283)	-0.029 (± 0.1829)	-0.022 (± 0.1667)		
Cycle 5 (Day 1) (n=324,260)	-0.019 (± 0.1622)	-0.016 (± 0.1826)		
Cycle 6 (Day 1) (n=300,229)	-0.025 (± 0.1787)	-0.003 (± 0.1967)		

Cycle 7 (Day 1) (n=276,202)	-0.018 (± 0.1651)	0.008 (± 0.1618)		
Cycle 8 (Day 1) (n=264,177)	-0.029 (± 0.1848)	0.002 (± 0.1731)		
Cycle 9 (Day 1) (n=249,155)	-0.029 (± 0.2021)	-0.011 (± 0.1662)		
Cycle 10 (Day 1) (n=236,152)	-0.025 (± 0.1935)	-0.018 (± 0.1617)		
Cycle 11 (Day 1) (n=228,138)	-0.020 (± 0.1854)	0.004 (± 0.1642)		
Cycle 12 (Day 1) (n=209,123)	-0.026 (± 0.1875)	-0.016 (± 0.1712)		
Cycle 13 (Day 1) (n=208,111)	-0.026 (± 0.1777)	-0.017 (± 0.1549)		
Cycle 14 (Day 1) (n=197,102)	-0.036 (± 0.1938)	-0.006 (± 0.1600)		
Cycle 15 (Day 1) (n=192,102)	-0.036 (± 0.1892)	0.018 (± 0.1487)		
Cycle 16 (Day 1) (n=175,95)	-0.044 (± 0.1757)	0.020 (± 0.1663)		
Cycle 17 (Day 1) (n=168,89)	-0.050 (± 0.1950)	-0.000 (± 0.1675)		
Cycle 18 (Day 1) (n=160,81)	-0.040 (± 0.1667)	-0.027 (± 0.1765)		
Cycle 19 (Day 1) (n=148,78)	-0.059 (± 0.1959)	0.003 (± 0.1665)		
Cycle 20 (Day 1) (n=143,71)	-0.050 (± 0.1942)	0.001 (± 0.1538)		
Cycle 21 (Day 1) (n=135,67)	-0.048 (± 0.1902)	-0.004 (± 0.1904)		
Cycle 22 (Day 1) (n=129,60)	0.037 (± 0.1919)	0.002 (± 0.1561)		
Cycle 23 (Day 1) (n=118,58)	-0.033 (± 0.2021)	-0.028 (± 0.1729)		
Cycle 24 (Day 1) (n=116,54)	-0.036 (± 0.1982)	0.004 (± 0.1618)		
Cycle 25 (Day 1) (n=112,54)	-0.019 (± 0.1825)	-0.007 (± 0.1678)		
Cycle 26 (Day 1) (n=111,48)	-0.039 (± 0.1927)	-0.009 (± 0.1471)		
Cycle 27 (Day 1) (n=107,45)	-0.046 (± 0.2233)	0.014 (± 0.1492)		
Cycle 28 (Day 1) (n=99,40)	-0.039 (± 0.2060)	-0.007 (± 0.1639)		
Cycle 29 (Day 1) (n=99,38)	-0.019 (± 0.2095)	0.017 (± 0.1601)		
Cycle 30 (Day 1) (n=94,36)	-0.032 (± 0.2244)	-0.003 (± 0.1557)		
Cycle 31 (Day 1) (n=90,35)	-0.042 (± 0.2246)	-0.009 (± 0.1508)		
Cycle 32 (Day 1) (n=86,31)	-0.044 (± 0.2095)	0.032 (± 0.1255)		
Cycle 33 (Day 1) (n=80,29)	-0.051 (± 0.2294)	-0.060 (± 0.3550)		
Cycle 34 (Day 1) (n=77,26)	-0.029 (± 0.1776)	0.038 (± 0.1558)		
Cycle 35 (Day 1) (n=66,26)	-0.010 (± 0.1442)	-0.002 (± 0.1610)		
Cycle 36 (Day 1) (n=65,24)	-0.016 (± 0.1599)	0.030 (± 0.1551)		
Cycle 37 (Day 1) (n=64,22)	-0.027 (± 0.1507)	0.052 (± 0.1601)		

Cycle 38 (Day 1) (n=59,21)	-0.016 (± 0.1459)	0.057 (± 0.1666)		
Cycle 39 (Day 1) (n=56,18)	-0.042 (± 0.1569)	0.052 (± 0.1386)		
Cycle 40 (Day 1) (n=55,18)	-0.021 (± 0.1484)	0.060 (± 0.1232)		
Cycle 41 (Day 1) (n=51,17)	-0.030 (± 0.1492)	0.056 (± 0.1853)		
Cycle 42 (Day 1) (n=48,17)	-0.021 (± 0.1634)	0.034 (± 0.1585)		
Cycle 43 (Day 1) (n=45,16)	-0.031 (± 0.1334)	0.011 (± 0.2062)		
Cycle 44 (Day 1) (n=48,16)	-0.028 (± 0.1300)	0.016 (± 0.2114)		
Cycle 45 (Day 1) (n=45,15)	-0.050 (± 0.1442)	0.007 (± 0.2191)		
Cycle 46 (Day 1) (n=43,15)	-0.042 (± 0.1380)	-0.007 (± 0.2495)		
Cycle 47 (Day 1) (n=39,13)	-0.019 (± 0.1240)	-0.015 (± 0.2335)		
Cycle 48 (Day 1) (n=39,12)	-0.025 (± 0.1566)	0.009 (± 0.2833)		
Cycle 49 (Day 1) (n=36,12)	-0.028 (± 0.1356)	0.010 (± 0.1873)		
Cycle 50 (Day 1) (n=34,12)	-0.028 (± 0.1359)	0.028 (± 0.2507)		
Cycle 51 (Day 1) (n=26,11)	-0.011 (± 0.1304)	-0.010 (± 0.2594)		
Cycle 52 (Day 1) (n=25,11)	-0.036 (± 0.1265)	-0.035 (± 0.2524)		
Cycle 53 (Day 1) (n=18,9)	-0.084 (± 0.1437)	0.048 (± 0.1308)		
Cycle 54 (Day 1) (n=18,8)	-0.040 (± 0.1425)	0.078 (± 0.1157)		
Cycle 55 (Day 1) (n=14,5)	-0.046 (± 0.1121)	0.051 (± 0.1060)		
Cycle 56 (Day 1) (n=9,2)	-0.083 (± 0.1081)	0.025 (± 0.1796)		
Cycle 57 (Day 1) (n=8,1)	-0.104 (± 0.1347)	0.031 (± 99999)		
Cycle 58 (Day 1) (n=7,1)	-0.078 (± 0.1408)	0.031 (± 99999)		
Cycle 59 (Day 1) (n=5,0)	-0.106 (± 0.1053)	88888 (± 88888)		
Cycle 60 (Day 1) (n=3,0)	-0.040 (± 0.1167)	88888 (± 88888)		
End of Treatment (n=275,297	-0.111 (± 0.2464)	-0.069 (± 0.2375)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Positive Anti-Drug Antibodies (ADA) and Neutralizing Antibodies (nAb) of Avelumab When Used in Combination With Axitinib

End point title	Number of Participants With Positive Anti-Drug Antibodies (ADA) and Neutralizing Antibodies (nAb) of Avelumab When Used in Combination With Axitinib[14]

End point description:

Immunogenicity analysis set included all participants who received at least one dose of study drug and who had at least one ADA/nAb sample collected for avelumab in “Avelumab + Axitinib” arm. Here "Participants Analyzed" signifies participants evaluable for this endpoint. This endpoint was not planned to be analyzed for ‘’Sunitinib’’ reporting group.

End point type	Secondary

End point timeframe:

From start of treatment until 30 days after the end of avelumab treatment (maximum up to approximately 90 months)

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint is specific to Avelumab and Axitinib; hence, only arm for Avelumab and Axitinib was included.

End point values	Avelumab + Axitinib			
Subject group type	Reporting group			
Number of subjects analysed	433			
Units: Participants				
ADA Positive	77			
nAb Positive	51			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in EQ-5D Visual Analogue Scale (VAS) Score

End point title	Change From Baseline in EQ-5D Visual Analogue Scale (VAS) Score

End point description:

EQ-VAS records the participant’s self-rated health status from 0 (worst imaginable health status) to 100 (best imaginable health status), where higher scores indicated better health status. FAS included all randomized participants. All participants reported under "Participants Analyzed" contributed data to the table; however, may not have evaluable data for every row. "n" signifies number of participants evaluable for the specified rows. "99999"= SD could not be calculated as only 1 participant was analyzed. “88888” mean and SD could not be calculated as 0 participant was analyzed.

End point type	Secondary

End point timeframe:

Baseline, Day 1 of Cycle 2 to Cycle 60, End of treatment (any Day from Day 1 of dosing; maximum up to approximately 89 months)

End point values	Avelumab + Axitinib	Sunitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	442	444		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Cycle 2 (Day 1) (n=381,347)	-0.9 (± 16.12)	-0.2 (± 15.85)		
Cycle 3 (Day 1) (n=355,312)	-0.4 (± 16.39)	0.4 (± 16.44)		

Cycle 4 (Day 1) (n=333,278)	-0.1 (± 17.23)	0.7 (± 17.26)		
Cycle 5 (Day 1) (n=322,258)	0.4 (± 16.66)	1.8 (± 16.16)		
Cycle 6 (Day 1) (n=296,224)	1.3 (± 16.05)	2.6 (± 15.35)		
Cycle 7 (Day 1) (n=275,197)	1.2 (± 16.34)	3.3 (± 14.91)		
Cycle 8 (Day 1) (n=266,174)	1.4 (± 16.54)	2.9 (± 13.84)		
Cycle 9 (Day 1) (n=246,154)	2.0 (± 16.06)	3.3 (± 13.77)		
Cycle 10 (Day 1) (n=233,150)	1.6 (± 15.12)	2.4 (± 14.46)		
Cycle 11 (Day 1) (n=225,135)	2.5 (± 15.70)	4.1 (± 12.91)		
Cycle 12 (Day 1) (n=207,121)	2.1 (± 14.72)	2.6 (± 14.59)		
Cycle 13 (Day 1) (n=205,110)	3.0 (± 14.39)	2.7 (± 14.29)		
Cycle 14 (Day 1) (n=196,101)	2.7 (± 15.07)	3.0 (± 13.98)		
Cycle 15 (Day 1) (n=192,101)	3.1 (± 14.97)	4.7 (± 13.63)		
Cycle 16 (Day 1) (n=175,94)	2.9 (± 15.08)	3.6 (± 14.02)		
Cycle 17 (Day 1) (n=167,88)	3.0 (± 15.44)	3.2 (± 12.88)		
Cycle 18 (Day 1) (n=162,82)	3.2 (± 15.31)	2.0 (± 13.69)		
Cycle 19 (Day 1) (n=147,78)	4.5 (± 15.61)	3.0 (± 13.10)		
Cycle 20 (Day 1) (n=142,71)	3.9 (± 15.15)	3.1 (± 12.58)		
Cycle 21 (Day 1) (n=132,67)	3.7 (± 16.30)	2.1 (± 13.00)		
Cycle 22 (Day 1) (n=128,60)	4.3 (± 16.43)	2.6 (± 12.82)		
Cycle 23 (Day 1) (n=117,58)	3.7 (± 16.90)	1.3 (± 15.16)		
Cycle 24 (Day 1) (n=115,55)	3.3 (± 18.70)	4.5 (± 13.45)		
Cycle 25 (Day 1) (n=113,54)	4.6 (± 15.28)	4.2 (± 14.42)		
Cycle 26 (Day 1) (n=111,48)	4.4 (± 17.10)	3.4 (± 13.00)		
Cycle 27 (Day 1) (n=106,45)	4.7 (± 16.59)	5.4 (± 13.43)		
Cycle 28 (Day 1) (n=98,40)	6.3 (± 16.08)	5.0 (± 13.84)		
Cycle 29 (Day 1) (n=98,38)	4.8 (± 15.44)	5.4 (± 14.24)		
Cycle 30 (Day 1) (n=94,36)	6.0 (± 15.78)	5.3 (± 14.61)		
Cycle 31 (Day 1) (n=89,35)	5.7 (± 15.42)	5.2 (± 14.88)		
Cycle 32 (Day 1) (n=85,31)	5.4 (± 16.35)	6.0 (± 13.57)		
Cycle 33 (Day 1) (n=79,29)	5.5 (± 16.07)	3.6 (± 20.61)		
Cycle 34 (Day 1) (n=76,26)	4.8 (± 15.25)	6.1 (± 15.91)		
Cycle 35 (Day 1) (n=65,26)	6.0 (± 14.53)	6.4 (± 15.61)		
Cycle 36 (Day 1) (n=64,24)	6.0 (± 15.63)	5.2 (± 17.11)		
Cycle 37 (Day 1) (n=63,22)	5.8 (± 14.63)	4.5 (± 15.86)		
Cycle 38 (Day 1) (n=58,20)	5.3 (± 14.58)	4.3 (± 17.58)		
Cycle 39 (Day 1) (n=56,18)	5.3 (± 14.04)	5.9 (± 15.75)		
Cycle 40 (Day 1) (n=54,18)	6.0 (± 15.00)	4.7 (± 18.17)		
Cycle 41 (Day 1) (n=52,17)	5.6 (± 13.69)	6.2 (± 18.37)		
Cycle 42 (Day 1) (n=47,17)	5.3 (± 13.68)	5.4 (± 18.19)		
Cycle 43 (Day 1) (n=44,16)	6.6 (± 11.64)	5.4 (± 20.14)		
Cycle 44 (Day 1) (n=47,16)	4.9 (± 13.38)	5.1 (± 19.77)		
Cycle 45 (Day 1) (n=44,15)	6.3 (± 12.55)	1.5 (± 17.97)		
Cycle 46 (Day 1) (n=41,15)	6.7 (± 13.25)	0.3 (± 19.31)		
Cycle 47 (Day 1) (n=38,13)	5.4 (± 11.10)	2.5 (± 18.07)		
Cycle 48 (Day 1) (n=38,12)	4.4 (± 11.73)	3.5 (± 21.77)		
Cycle 49 (Day 1) (n=35,12)	4.2 (± 12.21)	1.9 (± 21.42)		
Cycle 50 (Day 1) (n=33,12)	4.8 (± 13.07)	2.9 (± 20.53)		
Cycle 51 (Day 1) (n=26,10)	5.8 (± 12.36)	2.1 (± 22.93)		
Cycle 52 (Day 1) (n=25,11)	4.2 (± 11.37)	1.5 (± 19.94)		
Cycle 53 (Day 1) (n=18,9)	3.2 (± 11.43)	7.7 (± 16.22)		
Cycle 54 (Day 1) (n=18,8)	4.6 (± 11.54)	7.5 (± 13.34)		
Cycle 55 (Day 1) (n=14,5)	4.6 (± 11.65)	7.8 (± 17.89)		

Cycle 56 (Day 1) (n=9,2)	-0.6 (± 8.08)	-6.0 (± 5.66)		
Cycle 57 (Day 1) (n=8,1)	-1.9 (± 10.67)	-2.0 (± 99999)		
Cycle 58 (Day 1) (n=7,1)	-2.1 (± 8.59)	-2.0 (± 99999)		
Cycle 59 (Day 1) (n=5,0)	0.0 (± 9.35)	88888 (± 88888)		
Cycle 60 (Day 1) (n=3,0)	-1.7 (± 16.07)	88888 (± 88888)		
End of Treatment (n=277,296)	-5.0 (± 19.92)	-4.3 (± 19.63)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of study treatment until 90 days after last dose of study treatment (maximum up to approximately 92 months)

Adverse event reporting additional description:

Same event may appear as both non-SAE and SAE but are distinct events. An event may be categorized as serious in 1 participant and non-serious in another, or a participant may have experienced both SAE and non-SAE. For SAEs and non-SAEs safety analysis set was used. For All-cause mortality, FAS was used.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	v27.0

Reporting groups

Reporting group title	Sunitinib

Reporting group description:

Participants with aRCC received sunitinib 50 mg orally, QD on a schedule of 4 weeks on treatment followed by 2 weeks off treatment (schedule 4/2 in 6-week cycles). Each treatment cycle was of 42 days.

Reporting group title	Avelumab + Axitinib

Reporting group description:

Participants with advanced renal cell carcinoma (aRCC) received avelumab 10 milligram per kilogram (mg/kg), intravenously (IV) once every two weeks (Q2W) in a 6-week cycle plus axitinib 5 mg, orally twice daily (BID). Each treatment cycle was of 42 days.

Serious adverse events	Sunitinib	Avelumab + Axitinib	
Total subjects affected by serious adverse events			
subjects affected / exposed	166 / 439 (37.81%)	231 / 434 (53.23%)	
number of deaths (all causes)	296	284	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder transitional cell carcinoma			

subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			
subjects affected / exposed	1 / 439 (0.23%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal cancer			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial cancer			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive lobular breast carcinoma			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			

subjects affected / exposed	1 / 439 (0.23%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	1 / 439 (0.23%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour associated fever			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 439 (0.23%)	4 / 434 (0.92%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	1 / 439 (0.23%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm progression			
subjects affected / exposed	3 / 439 (0.68%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			

subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic dissection			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial insufficiency			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 439 (0.00%)	2 / 434 (0.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infarction			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			

subjects affected / exposed	3 / 439 (0.68%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	3 / 439 (0.68%)	3 / 434 (0.69%)	
occurrences causally related to treatment / all	2 / 3	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 439 (0.23%)	6 / 434 (1.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic shock			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism venous			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 439 (0.00%)	2 / 434 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral embolism			

subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 439 (0.00%)	4 / 434 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest discomfort			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 439 (0.00%)	6 / 434 (1.38%)	
occurrences causally related to treatment / all	0 / 0	4 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	7 / 439 (1.59%)	10 / 434 (2.30%)	
occurrences causally related to treatment / all	1 / 7	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 439 (0.23%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 439 (0.23%)	3 / 434 (0.69%)	
occurrences causally related to treatment / all	1 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised oedema			

subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	4 / 439 (0.91%)	3 / 434 (0.69%)	
occurrences causally related to treatment / all	2 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral swelling			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	6 / 439 (1.37%)	5 / 434 (1.15%)	
occurrences causally related to treatment / all	5 / 6	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 439 (0.00%)	2 / 434 (0.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Swelling			

subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Endometrial hyperplasia			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gynaecomastia			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Bronchial obstruction			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	2 / 439 (0.46%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			

subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	6 / 439 (1.37%)	8 / 434 (1.84%)	
occurrences causally related to treatment / all	1 / 6	5 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	3 / 439 (0.68%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	2 / 439 (0.46%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 439 (0.23%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			

subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	2 / 439 (0.46%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercapnia			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	2 / 439 (0.46%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	4 / 439 (0.91%)	5 / 434 (1.15%)	
occurrences causally related to treatment / all	1 / 4	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary toxicity			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	2 / 439 (0.46%)	3 / 434 (0.69%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			

subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Electrocardiogram abnormal			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 439 (0.00%)	2 / 434 (0.46%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood corticotrophin increased			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ejection fraction decreased			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram T wave inversion			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			

subjects affected / exposed	0 / 439 (0.00%)	2 / 434 (0.46%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial necrosis marker increased			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin I increased			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin increased			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Arterial injury			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 439 (0.23%)	2 / 434 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaw fracture			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Femur fracture			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 439 (0.00%)	2 / 434 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	0 / 439 (0.00%)	5 / 434 (1.15%)	
occurrences causally related to treatment / all	0 / 0	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 439 (0.23%)	2 / 434 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	1 / 439 (0.23%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 439 (0.23%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periprosthetic fracture			

subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 439 (0.23%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 439 (0.23%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Hydrocele			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiomyopathy			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 439 (0.00%)	11 / 434 (2.53%)	
occurrences causally related to treatment / all	0 / 0	3 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 439 (0.23%)	3 / 434 (0.69%)	
occurrences causally related to treatment / all	1 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Arrhythmia			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 439 (0.00%)	6 / 434 (1.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune myocarditis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorder			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			

subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac tamponade			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac ventricular thrombosis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	0 / 439 (0.00%)	6 / 434 (1.38%)	
occurrences causally related to treatment / all	0 / 0	5 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 439 (0.23%)	4 / 434 (0.92%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery occlusion			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			

subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial fibrosis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 439 (0.23%)	4 / 434 (0.92%)	
occurrences causally related to treatment / all	0 / 1	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocarditis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus bradycardia			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			

subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiovascular insufficiency			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	1 / 439 (0.23%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphasia			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ataxia			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain hypoxia			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolic stroke			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haematoma			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			

subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	4 / 439 (0.91%)	5 / 434 (1.15%)	
occurrences causally related to treatment / all	3 / 4	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic neuropathy			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 439 (0.23%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellar haemorrhage			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 439 (0.00%)	2 / 434 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	2 / 439 (0.46%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 439 (0.23%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial tumour haemorrhage			

subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	1 / 439 (0.23%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar radiculopathy			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyneuropathy			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Irregular sleep wake rhythm disorder			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			

subjects affected / exposed	1 / 439 (0.23%)	2 / 434 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	1 / 439 (0.23%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superficial siderosis of central nervous system			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	3 / 439 (0.68%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tremor			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	10 / 439 (2.28%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	6 / 10	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			

subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune thrombocytopenia			
subjects affected / exposed	1 / 439 (0.23%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	3 / 439 (0.68%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glaucoma			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Optic neuropathy			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Autoimmune pancreatitis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal distension			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal hernia			
subjects affected / exposed	0 / 439 (0.00%)	2 / 434 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal incarcerated hernia			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	12 / 439 (2.73%)	2 / 434 (0.46%)	
occurrences causally related to treatment / all	5 / 18	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphthous ulcer			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			

subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal necrosis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic erosive gastritis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 439 (0.23%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 439 (0.23%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 439 (0.00%)	3 / 434 (0.69%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			

subjects affected / exposed	1 / 439 (0.23%)	2 / 434 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	3 / 439 (0.68%)	12 / 434 (2.76%)	
occurrences causally related to treatment / all	2 / 3	11 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 439 (0.23%)	2 / 434 (0.46%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			

subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	3 / 439 (0.68%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	3 / 439 (0.68%)	3 / 434 (0.69%)	
occurrences causally related to treatment / all	3 / 3	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 439 (0.00%)	2 / 434 (0.46%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis necrotising			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumoperitoneum			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis			

subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 439 (0.23%)	2 / 434 (0.46%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal haemorrhage			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal haemorrhage			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	2 / 439 (0.46%)	3 / 434 (0.69%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	6 / 439 (1.37%)	4 / 434 (0.92%)	
occurrences causally related to treatment / all	6 / 6	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intussusception			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary dilatation			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary obstruction			

subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	0 / 439 (0.00%)	2 / 434 (0.46%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-mediated hepatitis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	2 / 439 (0.46%)	2 / 434 (0.46%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	2 / 439 (0.46%)	4 / 434 (0.92%)	
occurrences causally related to treatment / all	1 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis acute			
subjects affected / exposed	1 / 439 (0.23%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			

subjects affected / exposed	0 / 439 (0.00%)	2 / 434 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver disorder			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis acute			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis alcoholic			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder rupture			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash maculo-papular			

subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash papular			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scar pain			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin disorder			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splinter haemorrhages			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Exfoliative rash			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	1 / 439 (0.23%)	2 / 434 (0.46%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	9 / 439 (2.05%)	9 / 434 (2.07%)	
occurrences causally related to treatment / all	6 / 9	4 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus urinary			

subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	6 / 439 (1.37%)	5 / 434 (1.15%)	
occurrences causally related to treatment / all	3 / 6	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephropathy toxic			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 439 (0.23%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	2 / 439 (0.46%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal injury			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	3 / 439 (0.68%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			

subjects affected / exposed	0 / 439 (0.00%)	6 / 434 (1.38%)	
occurrences causally related to treatment / all	0 / 0	5 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperparathyroidism			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophysitis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothyroidism			
subjects affected / exposed	1 / 439 (0.23%)	2 / 434 (0.46%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pituitary apoplexy			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthyroidism			
subjects affected / exposed	0 / 439 (0.00%)	2 / 434 (0.46%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			

subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	3 / 439 (0.68%)	3 / 434 (0.69%)	
occurrences causally related to treatment / all	1 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	3 / 439 (0.68%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint range of motion decreased			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 439 (0.00%)	2 / 434 (0.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	1 / 439 (0.23%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	0 / 439 (0.00%)	2 / 434 (0.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			

subjects affected / exposed	2 / 439 (0.46%)	2 / 434 (0.46%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 439 (0.23%)	3 / 434 (0.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary sepsis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			

subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 439 (0.23%)	2 / 434 (0.46%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Actinomycosis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	3 / 439 (0.68%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine infection			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			

subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronavirus pneumonia			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal infection			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 439 (0.00%)	2 / 434 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related bacteraemia			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			

subjects affected / exposed	1 / 439 (0.23%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural infection			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	6 / 439 (1.37%)	6 / 434 (1.38%)	
occurrences causally related to treatment / all	1 / 6	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonsillar abscess			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			

subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung abscess			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal abscess			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 439 (0.46%)	2 / 434 (0.46%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sialoadenitis			

subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin graft infection			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	3 / 439 (0.68%)	2 / 434 (0.46%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	3 / 439 (0.68%)	5 / 434 (1.15%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella zoster virus infection			

subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 439 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	2 / 439 (0.46%)	5 / 434 (1.15%)	
occurrences causally related to treatment / all	2 / 2	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			

subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	2 / 439 (0.46%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 439 (0.00%)	4 / 434 (0.92%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemic hyperosmolar nonketotic syndrome			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 439 (0.23%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	0 / 439 (0.00%)	2 / 434 (0.46%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 439 (0.00%)	2 / 434 (0.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			

subjects affected / exposed	2 / 439 (0.46%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 1 diabetes mellitus			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophagia			
subjects affected / exposed	0 / 439 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Sunitinib	Avelumab + Axitinib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	433 / 439 (98.63%)	429 / 434 (98.85%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	19 / 439 (4.33%)	26 / 434 (5.99%)	
occurrences (all)	19	35	
Hypertension			
subjects affected / exposed	168 / 439 (38.27%)	236 / 434 (54.38%)	
occurrences (all)	274	481	
General disorders and administration site conditions			
Mucosal inflammation			
subjects affected / exposed	64 / 439 (14.58%)	69 / 434 (15.90%)	
occurrences (all)	101	122	
Oedema peripheral			

subjects affected / exposed	58 / 439 (13.21%)	55 / 434 (12.67%)	
occurrences (all)	84	81	
Pain			
subjects affected / exposed	23 / 439 (5.24%)	22 / 434 (5.07%)	
occurrences (all)	25	23	
Pyrexia			
subjects affected / exposed	65 / 439 (14.81%)	74 / 434 (17.05%)	
occurrences (all)	87	104	
Malaise			
subjects affected / exposed	23 / 439 (5.24%)	17 / 434 (3.92%)	
occurrences (all)	56	24	
Influenza like illness			
subjects affected / exposed	22 / 439 (5.01%)	34 / 434 (7.83%)	
occurrences (all)	32	50	
Fatigue			
subjects affected / exposed	194 / 439 (44.19%)	205 / 434 (47.24%)	
occurrences (all)	333	497	
Chills			
subjects affected / exposed	38 / 439 (8.66%)	75 / 434 (17.28%)	
occurrences (all)	45	90	
Chest pain			
subjects affected / exposed	12 / 439 (2.73%)	22 / 434 (5.07%)	
occurrences (all)	13	26	
Asthenia			
subjects affected / exposed	83 / 439 (18.91%)	83 / 434 (19.12%)	
occurrences (all)	183	200	
Respiratory, thoracic and mediastinal disorders			
Nasal congestion			
subjects affected / exposed	20 / 439 (4.56%)	28 / 434 (6.45%)	
occurrences (all)	24	34	
Epistaxis			
subjects affected / exposed	54 / 439 (12.30%)	48 / 434 (11.06%)	
occurrences (all)	78	66	
Dyspnoea exertional			

subjects affected / exposed	21 / 439 (4.78%)	33 / 434 (7.60%)	
occurrences (all)	28	53	
Dyspnoea			
subjects affected / exposed	68 / 439 (15.49%)	106 / 434 (24.42%)	
occurrences (all)	94	193	
Dysphonia			
subjects affected / exposed	20 / 439 (4.56%)	148 / 434 (34.10%)	
occurrences (all)	23	225	
Cough			
subjects affected / exposed	103 / 439 (23.46%)	147 / 434 (33.87%)	
occurrences (all)	146	251	
Rhinorrhoea			
subjects affected / exposed	14 / 439 (3.19%)	37 / 434 (8.53%)	
occurrences (all)	20	47	
Productive cough			
subjects affected / exposed	15 / 439 (3.42%)	23 / 434 (5.30%)	
occurrences (all)	17	34	
Oropharyngeal pain			
subjects affected / exposed	38 / 439 (8.66%)	57 / 434 (13.13%)	
occurrences (all)	44	66	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	37 / 439 (8.43%)	51 / 434 (11.75%)	
occurrences (all)	43	62	
Anxiety			
subjects affected / exposed	24 / 439 (5.47%)	38 / 434 (8.76%)	
occurrences (all)	25	41	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	50 / 439 (11.39%)	94 / 434 (21.66%)	
occurrences (all)	91	219	
Amylase increased			
subjects affected / exposed	16 / 439 (3.64%)	34 / 434 (7.83%)	
occurrences (all)	33	57	
Aspartate aminotransferase increased			

subjects affected / exposed	59 / 439 (13.44%)	83 / 434 (19.12%)	
occurrences (all)	112	164	
Blood alkaline phosphatase increased			
subjects affected / exposed	24 / 439 (5.47%)	21 / 434 (4.84%)	
occurrences (all)	32	40	
Blood bilirubin increased			
subjects affected / exposed	20 / 439 (4.56%)	22 / 434 (5.07%)	
occurrences (all)	28	44	
Blood cholesterol increased			
subjects affected / exposed	16 / 439 (3.64%)	23 / 434 (5.30%)	
occurrences (all)	41	58	
Blood corticotrophin increased			
subjects affected / exposed	2 / 439 (0.46%)	23 / 434 (5.30%)	
occurrences (all)	4	26	
Blood creatine phosphokinase increased			
subjects affected / exposed	14 / 439 (3.19%)	26 / 434 (5.99%)	
occurrences (all)	24	52	
Blood creatinine increased			
subjects affected / exposed	37 / 439 (8.43%)	64 / 434 (14.75%)	
occurrences (all)	63	131	
Blood thyroid stimulating hormone increased			
subjects affected / exposed	25 / 439 (5.69%)	37 / 434 (8.53%)	
occurrences (all)	29	46	
Eastern Cooperative Oncology Group performance status worsened			
subjects affected / exposed	23 / 439 (5.24%)	13 / 434 (3.00%)	
occurrences (all)	33	26	
Ejection fraction decreased			
subjects affected / exposed	17 / 439 (3.87%)	48 / 434 (11.06%)	
occurrences (all)	21	74	
Gamma-glutamyltransferase increased			
subjects affected / exposed	21 / 439 (4.78%)	39 / 434 (8.99%)	
occurrences (all)	39	96	
Lipase increased			

subjects affected / exposed	27 / 439 (6.15%)	53 / 434 (12.21%)	
occurrences (all)	59	114	
Neutrophil count decreased			
subjects affected / exposed	47 / 439 (10.71%)	5 / 434 (1.15%)	
occurrences (all)	325	10	
Platelet count decreased			
subjects affected / exposed	63 / 439 (14.35%)	10 / 434 (2.30%)	
occurrences (all)	186	22	
Weight decreased			
subjects affected / exposed	46 / 439 (10.48%)	112 / 434 (25.81%)	
occurrences (all)	64	192	
White blood cell count decreased			
subjects affected / exposed	38 / 439 (8.66%)	4 / 434 (0.92%)	
occurrences (all)	191	9	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	13 / 439 (2.96%)	26 / 434 (5.99%)	
occurrences (all)	16	28	
Infusion related reaction			
subjects affected / exposed	0 / 439 (0.00%)	54 / 434 (12.44%)	
occurrences (all)	0	70	
Nervous system disorders			
Taste disorder			
subjects affected / exposed	48 / 439 (10.93%)	24 / 434 (5.53%)	
occurrences (all)	57	28	
Paraesthesia			
subjects affected / exposed	19 / 439 (4.33%)	25 / 434 (5.76%)	
occurrences (all)	26	27	
Headache			
subjects affected / exposed	85 / 439 (19.36%)	122 / 434 (28.11%)	
occurrences (all)	127	154	
Dysgeusia			
subjects affected / exposed	107 / 439 (24.37%)	48 / 434 (11.06%)	
occurrences (all)	153	58	
Dizziness			

subjects affected / exposed	52 / 439 (11.85%)	72 / 434 (16.59%)	
occurrences (all)	70	97	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	89 / 439 (20.27%)	17 / 434 (3.92%)	
occurrences (all)	259	41	
Neutropenia			
subjects affected / exposed	90 / 439 (20.50%)	9 / 434 (2.07%)	
occurrences (all)	528	13	
Leukopenia			
subjects affected / exposed	27 / 439 (6.15%)	1 / 434 (0.23%)	
occurrences (all)	56	3	
Anaemia			
subjects affected / exposed	116 / 439 (26.42%)	41 / 434 (9.45%)	
occurrences (all)	331	75	
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	87 / 439 (19.82%)	51 / 434 (11.75%)	
occurrences (all)	119	66	
Dry mouth			
subjects affected / exposed	25 / 439 (5.69%)	42 / 434 (9.68%)	
occurrences (all)	29	54	
Diarrhoea			
subjects affected / exposed	228 / 439 (51.94%)	303 / 434 (69.82%)	
occurrences (all)	581	1475	
Constipation			
subjects affected / exposed	73 / 439 (16.63%)	97 / 434 (22.35%)	
occurrences (all)	102	144	
Abdominal pain upper			
subjects affected / exposed	36 / 439 (8.20%)	34 / 434 (7.83%)	
occurrences (all)	46	47	
Gastrooesophageal reflux disease			
subjects affected / exposed	44 / 439 (10.02%)	22 / 434 (5.07%)	
occurrences (all)	59	27	
Abdominal pain			

subjects affected / exposed	57 / 439 (12.98%)	90 / 434 (20.74%)	
occurrences (all)	83	119	
Toothache			
subjects affected / exposed	12 / 439 (2.73%)	25 / 434 (5.76%)	
occurrences (all)	13	32	
Stomatitis			
subjects affected / exposed	113 / 439 (25.74%)	117 / 434 (26.96%)	
occurrences (all)	207	237	
Oral pain			
subjects affected / exposed	21 / 439 (4.78%)	33 / 434 (7.60%)	
occurrences (all)	26	57	
Nausea			
subjects affected / exposed	185 / 439 (42.14%)	186 / 434 (42.86%)	
occurrences (all)	320	322	
Haemorrhoids			
subjects affected / exposed	31 / 439 (7.06%)	21 / 434 (4.84%)	
occurrences (all)	41	23	
Vomiting			
subjects affected / exposed	99 / 439 (22.55%)	101 / 434 (23.27%)	
occurrences (all)	177	196	
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	162 / 439 (36.90%)	160 / 434 (36.87%)	
occurrences (all)	431	558	
Erythema			
subjects affected / exposed	17 / 439 (3.87%)	24 / 434 (5.53%)	
occurrences (all)	20	31	
Dry skin			
subjects affected / exposed	52 / 439 (11.85%)	60 / 434 (13.82%)	
occurrences (all)	64	93	
Alopecia			
subjects affected / exposed	17 / 439 (3.87%)	22 / 434 (5.07%)	
occurrences (all)	19	22	
Yellow skin			

subjects affected / exposed	28 / 439 (6.38%)	1 / 434 (0.23%)	
occurrences (all)	30	1	
Skin exfoliation			
subjects affected / exposed	23 / 439 (5.24%)	16 / 434 (3.69%)	
occurrences (all)	35	16	
Rash pruritic			
subjects affected / exposed	15 / 439 (3.42%)	27 / 434 (6.22%)	
occurrences (all)	19	30	
Rash maculo-papular			
subjects affected / exposed	11 / 439 (2.51%)	29 / 434 (6.68%)	
occurrences (all)	13	50	
Rash			
subjects affected / exposed	54 / 439 (12.30%)	74 / 434 (17.05%)	
occurrences (all)	74	117	
Pruritus			
subjects affected / exposed	29 / 439 (6.61%)	96 / 434 (22.12%)	
occurrences (all)	36	146	
Hair colour changes			
subjects affected / exposed	29 / 439 (6.61%)	2 / 434 (0.46%)	
occurrences (all)	30	2	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	19 / 439 (4.33%)	35 / 434 (8.06%)	
occurrences (all)	39	89	
Pollakiuria			
subjects affected / exposed	9 / 439 (2.05%)	23 / 434 (5.30%)	
occurrences (all)	10	25	
Haematuria			
subjects affected / exposed	25 / 439 (5.69%)	17 / 434 (3.92%)	
occurrences (all)	45	22	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	89 / 439 (20.27%)	135 / 434 (31.11%)	
occurrences (all)	102	159	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	83 / 439 (18.91%)	157 / 434 (36.18%)	
occurrences (all)	133	298	
Back pain			
subjects affected / exposed	80 / 439 (18.22%)	118 / 434 (27.19%)	
occurrences (all)	106	174	
Bone pain			
subjects affected / exposed	18 / 439 (4.10%)	23 / 434 (5.30%)	
occurrences (all)	23	30	
Muscle spasms			
subjects affected / exposed	20 / 439 (4.56%)	28 / 434 (6.45%)	
occurrences (all)	38	40	
Musculoskeletal chest pain			
subjects affected / exposed	22 / 439 (5.01%)	36 / 434 (8.29%)	
occurrences (all)	25	44	
Myalgia			
subjects affected / exposed	32 / 439 (7.29%)	59 / 434 (13.59%)	
occurrences (all)	35	100	
Neck pain			
subjects affected / exposed	11 / 439 (2.51%)	27 / 434 (6.22%)	
occurrences (all)	12	31	
Pain in extremity			
subjects affected / exposed	63 / 439 (14.35%)	87 / 434 (20.05%)	
occurrences (all)	86	132	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	38 / 439 (8.66%)	58 / 434 (13.36%)	
occurrences (all)	48	94	
Upper respiratory tract infection			
subjects affected / exposed	19 / 439 (4.33%)	40 / 434 (9.22%)	
occurrences (all)	26	80	
Urinary tract infection			
subjects affected / exposed	15 / 439 (3.42%)	32 / 434 (7.37%)	
occurrences (all)	18	49	
Metabolism and nutrition disorders			

Decreased appetite			
subjects affected / exposed	144 / 439 (32.80%)	141 / 434 (32.49%)	
occurrences (all)	211	242	
Dehydration			
subjects affected / exposed	7 / 439 (1.59%)	24 / 434 (5.53%)	
occurrences (all)	12	34	
Hyperglycaemia			
subjects affected / exposed	21 / 439 (4.78%)	31 / 434 (7.14%)	
occurrences (all)	33	56	
Hyperkalaemia			
subjects affected / exposed	25 / 439 (5.69%)	25 / 434 (5.76%)	
occurrences (all)	43	40	
Hypertriglyceridaemia			
subjects affected / exposed	31 / 439 (7.06%)	49 / 434 (11.29%)	
occurrences (all)	97	158	
Hypokalaemia			
subjects affected / exposed	25 / 439 (5.69%)	26 / 434 (5.99%)	
occurrences (all)	45	81	
Hypomagnesaemia			
subjects affected / exposed	25 / 439 (5.69%)	35 / 434 (8.06%)	
occurrences (all)	75	57	
Hyponatraemia			
subjects affected / exposed	28 / 439 (6.38%)	29 / 434 (6.68%)	
occurrences (all)	43	43	
Hypophosphataemia			
subjects affected / exposed	41 / 439 (9.34%)	49 / 434 (11.29%)	
occurrences (all)	111	112	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 October 2015	Amendment 1: As per FDA request: Schedule of Activities (SoA) table and footnotes were updated as follow: Creatinine kinase and troponin measurements have been added. They will be performed along with any clinically indicated ECG assessment performed beyond Cycle 1. Section 7.1.5 and Table 9 were updated accordingly. Extend the duration of tumor assessment monitoring using the 6-week interval up to 18 months after randomization. Sections 3.1.2 and 7.7 were updated accordingly. Add PRO assessments also during Follow-Up. Sections 7.2.1 and 7.2.2 were updated accordingly. Section 9.3.2 language was updated to clarify how the analysis will be performed.
24 May 2016	Amendment 2: As per FDA request, clarification about the treatment of symptoms of avelumab infusion-related reactions was added to Section 5.4.6.7. Details on the type and dosages of medications recommended for the treatment of avelumab infusion-related reactions were added to Appendix 8. As per the requests from the EUcountries participating in the Voluntary Harmonisation Procedure, the following sections were amended: Sections 1.2.2.2. Axitinib and 1.2.2.3. Sunitinib Malate were updated indicating that Reference Safety Information (RSI) can be found in Section 7.8 of the respective Investigators Brochures. Location of RSI for avelumab was also specified (Section 1.2.2.1). Section 12.1. Institutional Review Board/Ethics Committee text was updated to clarify that only changes of study documents classified as “substantial” should be prospectively approved by IRBs/ECs. Section 12.2 Ethical Conduct of the Study. The version of the Declaration of Helsinki was updated.
30 August 2016	Amendment 3: As per the requests from the EU countries participating in the Voluntary Harmonisation Procedure, the following sections were amended: Sections 1.2.3 Rationale for Studying Avelumab in Combination with Axitinib, and 1.3 Summary of Risk/Benefit Assessment. Text was updated to include preliminary data from the ongoing Phase 1b study of axitinib in combination with avelumab in aRCC (Study B9991002). Section 2 Study Objectives and Endpoints. The assessment of PFS on next-line therapy (PFS2), time to treatment discontinuation/failure due to toxicity, and proportion of patients who discontinued treatment due to toxicity were added to secondary objectives in Section 2.1, and associated endpoints were added to the secondary endpoints Section 2.2. Sections 9.3.2 Analysis of Secondary Endpoints and 9.5 Safety Analysis were updated accordingly.
08 December 2016	Amendment 4: Exclusion Criterion (EC) No.19 was updated and new ECs (EC No. 20 and 21) were added to exclude patients with pre-existing cardiac conditions within 12 months prior to enrollment, or evidence of cardiac involvement with tumor, to better discriminate between drug-related toxicity and underlying heart disease. An independent cardiac events adjudication committee was also established to review selected cardiac adverse events reported in the study in order to confirm the diagnosis and relationship to study treatment. This will enable a comprehensive evaluation of the cardiac safety profile of the combination of avelumab and axitinib. Based on a recent publication (Johnson et al, N Engl J Med 2016; 375:1749-55), cardiac enzyme evaluation was extended up to Cycle 3.
12 June 2017	Amendment 5: The primary objective of the study was changed to demonstrate superiority of avelumab in combination with axitinib compared to sunitinib alone based on Progression Free Survival (PFS) by Blinded Independent Central Review (BICR) or Overall Survival (OS) in PD-L1 positive patients based on recent publications (Motzer RJ et al, N Engl J Med 2015; 373:1803-13; McDermott D et al, J Clin Oncol 35, 2017, suppl 6S; abstract 431). Protocol Summary, Sections 1.2.3 (Rationale for testing avelumab in combination with axitinib in RCC), 2 (Objectives & Endpoints), 6.4 (End of the Study) and Data Analysis /Statistical Sections 9.1, 9.2, 9.3, 9.3.1, 9.3.2, 9.6 were updated.

26 June 2018	Amendment 6: Interim Analysis (IA): IA3 for OS was added to occur 15 months after the primary analysis for PFS (IA2 for OS) due to the fact that the aggregate number of deaths observed in the study as of the date of this amendment is substantially lower than that expected per protocol, leading to a substantially longer duration between the originally expected timing of the primary analysis for PFS (IA2 for OS) and the primary analysis for OS. Protocol summary, Section 9.1 (Sample Size Determination) and Section 9.6 (Interim Analysis).
04 September 2018	Amendment 7: Schedule of Activities (SoA) for Screening/Study Treatment Period was updated specifying blood samples for avelumab pharmacokinetics (PK) and for testing avelumab immunogenicity (ie, anti-avelumab antibodies and neutralizing antibodies) will be collected up to Cycle 16 and not thereafter since samples collected so far are sufficient to properly characterize avelumab PK and assess immunogenicity. SoA Footnotes 24 and 28 were updated accordingly.
02 January 2020	Amendment 8: Reduction of safety assessments: The safety profile of the combination avelumab plus axitinib is generally tolerable, manageable, and consistent with the known safety profiles of avelumab and axitinib when administered as monotherapies, per interim analysis (IA) 1 and 2 results (cut off dates: 20 June 2018 and 28 January 2019). All patients who are still receiving treatment with study drug/s, have been on treatment for more than 1.8 years. . As per above and in order to reduce the burden to participants and sites, the frequency of safety assessments was reduced. A new Schedule of Activities (SoA) table, and a new table for laboratory tests “Laboratories Safety Assessments” were added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported