Clinical trial results:
A Phase III, Open-Label, Randomized Study of Atezolizumab (Anti-PD-L1 Antibody) in Combination with Bevacizumab versus Sunitinib in Patients with Untreated Advanced Renal Cell Carcinoma

Summary

EudraCT number	2014-004684-20
Trial protocol	ES GB DK CZ DE FR PL IT
Global end of trial date	

Results information

Result version number	v1
This version publication date	07 September 2018
First version publication date	07 September 2018

Trial information

Trial identification

Sponsor protocol code	WO29637

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02420821
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.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	Interim
Date of interim/final analysis	29 September 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 September 2017
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of "Atezolizumab + Bevacizumab" compared with "Sunitinib" as measured by the coprimary endpoints of investigator-assessed progression-free survival (PFS) in the immune cell (IC)1/2/3 population per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) and overall survival (OS) in the Intent-To-Treat (ITT) Population.

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice (GCP). Approval from the Independent Ethics Committee/Institutional Review Board (IEC/IRB) was obtained before study start and was documented in a letter to the Investigator specifying the date on which the committee met and granted the approval. The Sponsor also obtained approval from the relevant Competent Authority prior to starting the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 May 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	4 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Japan: 61
Country: Number of subjects enrolled	Korea, Republic of: 59
Country: Number of subjects enrolled	Singapore: 8
Country: Number of subjects enrolled	Thailand: 16
Country: Number of subjects enrolled	Taiwan: 9
Country: Number of subjects enrolled	Brazil: 15
Country: Number of subjects enrolled	Mexico: 13
Country: Number of subjects enrolled	Bosnia and Herzegovina: 3
Country: Number of subjects enrolled	Czech Republic: 30
Country: Number of subjects enrolled	Poland: 26
Country: Number of subjects enrolled	Russian Federation: 57
Country: Number of subjects enrolled	Turkey: 23
Country: Number of subjects enrolled	Canada: 59
Country: Number of subjects enrolled	United States: 122
Country: Number of subjects enrolled	Australia: 51
Country: Number of subjects enrolled	Germany: 18
Country: Number of subjects enrolled	Denmark: 33

Country: Number of subjects enrolled	Spain: 83
Country: Number of subjects enrolled	France: 52
Country: Number of subjects enrolled	United Kingdom: 95
Country: Number of subjects enrolled	Italy: 82
Worldwide total number of subjects	915
EEA total number of subjects	419

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)	587
From 65 to 84 years	327
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 1228 participants were screened, out of which, 915 participants were enrolled into 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	Sunitinib

Arm description:

Participants received sunitinib at a dose of 50 milligrams (mg) administered orally via capsules once daily on Days 1 to 28 of each 42-day cycle until loss of clinical benefit in the opinion of the investigator, unacceptable toxicity or symptomatic deterioration attributed to disease progression (PD) as determined by the investigator, withdrawal of consent, or death, whichever occurred first.

Arm type	Active comparator
Investigational medicinal product name	Sunitinib
Investigational medicinal product code	
Other name	Sutent
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Sunitinib was administered at a dose of 50 mg once daily, orally via capsule, on Day 1 through Day 28 of each 42-day cycle.

Arm title	Atezolizumab + Bevacizumab

Arm description:

Participants received atezolizumab at a dose of 1200 mg and bevacizumab at a dose of 15 milligrams per kilogram (mg/kg) administered via intravenous (IV) infusions on Day 1 and Day 22 of each 42-day cycle until loss of clinical benefit in the opinion of the investigator, unacceptable toxicity or symptomatic deterioration attributed to PD as determined by the investigator, withdrawal of consent, or death, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	Avastin
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab was administered at a dose of 15 mg/kg via IV infusion on Days 1 and 22 of each 42-day cycle.

Investigational medicinal product name	Atezolizumab
Investigational medicinal product code	
Other name	Tecentriq, MPDL3280A
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Atezolizumab was administered at a fixed dose of 1200 mg via IV infusion on Days 1 and 22 of each 42-day cycle.

Number of subjects in period 1	Sunitinib	Atezolizumab + Bevacizumab
Started	461	454
Completed	293	317
Not completed	168	137
Physician decision	5	2
Consent withdrawn by subject	31	17
Death	129	116
Non-compliance	1	2
Lost to follow-up	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Sunitinib
Reporting group description:	
Participants received sunitinib at a dose of 50 milligrams (mg) administered orally via capsules once daily on Days 1 to 28 of each 42-day cycle until loss of clinical benefit in the opinion of the investigator, unacceptable toxicity or symptomatic deterioration attributed to disease progression (PD) as determined by the investigator, withdrawal of consent, or death, whichever occurred first.	
Reporting group title	Atezolizumab + Bevacizumab
Reporting group description:	
Participants received atezolizumab at a dose of 1200 mg and bevacizumab at a dose of 15 milligrams per kilogram (mg/kg) administered via intravenous (IV) infusions on Day 1 and Day 22 of each 42-day cycle until loss of clinical benefit in the opinion of the investigator, unacceptable toxicity or symptomatic deterioration attributed to PD as determined by the investigator, withdrawal of consent, or death, whichever occurred first.	

Reporting group values	Sunitinib	Atezolizumab + Bevacizumab	Total
Number of subjects	461	454	915
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	59.9	61.6	
standard deviation	± 9.9	± 10.4	-
Sex: Female, Male Units: Subjects			
Female	109	137	246
Male	352	317	669
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	2	3
Asian	77	94	171
Native Hawaiian or Other Pacific Islander	0	1	1
Black or African American	4	1	5
White	334	326	660
More than one race	0	0	0
Unknown or Not Reported	45	30	75
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	32	25	57
Not Hispanic or Latino	386	391	777
Unknown or Not Reported	43	38	81

End points

End points reporting groups

Reporting group title	Sunitinib

Reporting group description:

Participants received sunitinib at a dose of 50 milligrams (mg) administered orally via capsules once daily on Days 1 to 28 of each 42-day cycle until loss of clinical benefit in the opinion of the investigator, unacceptable toxicity or symptomatic deterioration attributed to disease progression (PD) as determined by the investigator, withdrawal of consent, or death, whichever occurred first.

Reporting group title	Atezolizumab + Bevacizumab

Reporting group description:

Participants received atezolizumab at a dose of 1200 mg and bevacizumab at a dose of 15 milligrams per kilogram (mg/kg) administered via intravenous (IV) infusions on Day 1 and Day 22 of each 42-day cycle until loss of clinical benefit in the opinion of the investigator, unacceptable toxicity or symptomatic deterioration attributed to PD as determined by the investigator, withdrawal of consent, or death, whichever occurred first.

Primary: Percentage of Participants with PD as Determined by the Investigator According to RECIST v1.1 or Death from Any Cause in Programmed Death-Ligand 1 (PD-L1)-Selected Population

End point title	Percentage of Participants with PD as Determined by the Investigator According to RECIST v1.1 or Death from Any Cause in Programmed Death-Ligand 1 (PD-L1)-Selected Population[1]

End point description:

Tumor response was assessed by the investigator according to RECIST v1.1. The PD was defined as greater than or equal to (>/=) 20 percent (%) relative increase in the sum of diameters (SoD) of all target lesions (TLs), taking as reference the smallest SoD on study, including baseline, and an absolute increase of >/=5 millimeters (mm); >/=1 new lesion(s); and/or unequivocal progression of existing non-TLs. Analysis was performed on the PD-L1-Selected Population, which included all randomized participants whose PD-L1 status was IC1/2/3 at the time of randomization.

End point type	Primary

End point timeframe:

Baseline until documented PD or death, whichever occurred first (until data cut-off date 29 September 2017, up to approximately 24 months)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Results for this outcome measure were reported descriptively and were not planned to be analyzed for statistically significant differences between the arms.

End point values	Sunitinib	Atezolizumab + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184	178		
Units: percentage of participants				
number (not applicable)	69.6	58.4		

Statistical analyses

No statistical analyses for this end point

Primary: Progression-Free Survival (PFS) as Determined by the Investigator According to RECIST v1.1 in PD-L1-Selected Population

End point title	Progression-Free Survival (PFS) as Determined by the Investigator According to RECIST v1.1 in PD-L1-Selected Population

End point description:

PFS was defined as the time from randomization to PD, as determined by the investigator per RECIST v1.1, or death from any cause, whichever occurred first. PD: >/=20% relative increase in the SoD of all TLs, taking as reference the smallest SoD on study, including baseline, and an absolute increase of >/=5 mm; >/=1 new lesion(s); and/or unequivocal progression of non-TLs. Participants without PFS event were censored at the last tumor assessment date. Participants with no post-baseline tumor assessments were censored at the randomization date + 1 day. Participants with a PFS event who missed >/=2 scheduled assessments immediately prior to the PFS event were censored at the last tumor assessment prior to the missed visits. Median PFS was estimated by Kaplan-Meier method and 95% confidence interval (CI) was assessed using the method of Brookmeyer and Crowley. Analysis was performed on the PD-L1-Selected Population.

End point type	Primary

End point timeframe:

Baseline until documented PD or death, whichever occurred first (until data cut-off date 29 September 2017, up to approximately 24 months)

End point values	Sunitinib	Atezolizumab + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184	178		
Units: months				
median (confidence interval 95%)	7.5 (6.8 to 9.7)	11.2 (8.6 to 14.3)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Stratified Analysis: Strata were presence of liver metastases, Motzer score, PD-L1 level per interactive voice/web response system (IxRS).

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	362
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.0205
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	0.95

Notes:

[2] - Hazard ratio was estimated by Cox regression.

Primary: Percentage of Participants Who Died of Any Cause in ITT Population

End point title	Percentage of Participants Who Died of Any Cause in ITT Population[3]

End point description:

Percentage of participants who died of any cause was reported. Analysis was performed on the ITT Population, which included all randomized participants whether or not the assigned study treatment was received.

End point type	Primary

End point timeframe:

Baseline until death from any cause (until data cut-off date 29 September 2017, up to approximately 27 months)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Results for this outcome measure were reported descriptively and were not planned to be analyzed for statistically significant differences between the arms.

End point values	Sunitinib	Atezolizumab + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	461	454		
Units: percentage of participants				
number (not applicable)	30.6	27.1		

Statistical analyses

No statistical analyses for this end point

Primary: Overall Survival (OS) in ITT Population

End point title	Overall Survival (OS) in ITT Population

End point description:

OS was defined as the time from randomization to death due to any cause. Participants who were not reported as having died at the date of analysis were censored at the date when they were last known to be alive. Participants who did not have post-baseline information were censored at the date of randomization + 1 day. Median OS was estimated by Kaplan-Meier method and 95% CI was assessed using the method of Brookmeyer and Crowley. Analysis was performed on the ITT Population. The data '99999' in the results signifies that median and corresponding 95% CI could not be estimated due to high number of censored participants.

End point type	Primary

End point timeframe:

Baseline until death from any cause (until data cut-off date 29 September 2017, up to approximately 27 months)

End point values	Sunitinib	Atezolizumab + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	461	454		
Units: months				
median (confidence interval 95%)	99999 (23.3 to 99999)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Stratified Analysis: Strata were presence of liver metastases, Motzer score, PD-L1 level per interactive voice/web response system (IxRS).

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	915
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.0895
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	1.03

Notes:

[4] - Hazard ratio was estimated by Cox regression.

Secondary: Percentage of Participants Who Died of Any Cause in PD-L1-Selected Population

End point title	Percentage of Participants Who Died of Any Cause in PD-L1-Selected Population

End point description:

Percentage of participants who died of any cause was reported. Analysis was performed on the PD-L1-Selected Population.

End point type	Secondary

End point timeframe:

Baseline until death from any cause (until data cut-off date 29 September 2017, up to approximately 27 months)

End point values	Sunitinib	Atezolizumab + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184	178		
Units: percentage of participants				
number (not applicable)	34.8	25.3		

Statistical analyses

No statistical analyses for this end point

Secondary: OS in PD-L1-Selected Population

End point title	OS in PD-L1-Selected Population

End point description:

OS was defined as the time from randomization to death due to any cause. Participants who were not reported as having died at the date of analysis were censored at the date when they were last known to be alive. Participants who did not have post-baseline information were censored at the date of randomization + 1 day. Median OS was estimated by Kaplan-Meier method and 95% CI was assessed using the method of Brookmeyer and Crowley. Analysis was performed on the PD-L1-Selected Population. The data '99999' in the results signifies that median and/or corresponding 95% CI could not be estimated due to high number of censored participants.

End point type	Secondary

End point timeframe:

Baseline until death from any cause (until data cut-off date 29 September 2017, up to approximately 27 months)

End point values	Sunitinib	Atezolizumab + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184	178		
Units: months				
median (confidence interval 95%)	23.3 (21.3 to 99999)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Stratified Analysis: Strata were presence of liver metastases, Motzer score, PD-L1 level per interactive voice/web response system (IxRS).

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab

Number of subjects included in analysis	362
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.047
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	1

Notes:

[5] - Hazard ratio was estimated by Cox regression.

Secondary: Percentage of Participants with PD as Determined by an Independent Review Committee (IRC) According to RECIST v1.1 or Death from Any Cause in ITT Population

End point title	Percentage of Participants with PD as Determined by an Independent Review Committee (IRC) According to RECIST v1.1 or Death from Any Cause in ITT Population

End point description:

Tumor response was assessed by an IRC according to RECIST v1.1. PD was defined as >/=20% relative increase in the SoD of all TLs, taking as reference the smallest SoD on study, including baseline, and an absolute increase of >/=5 mm; >/=1 new lesion(s); and/or unequivocal progression of non-TLs. Analysis was performed on the ITT Population.

End point type	Secondary

End point timeframe:

Baseline until documented PD or death, whichever occurred first (until data cut-off date 29 September 2017, up to approximately 24 months)

End point values	Sunitinib	Atezolizumab + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	461	454		
Units: percentage of participants				
number (not applicable)	63.6	60.4		

Statistical analyses

No statistical analyses for this end point

Secondary: PFS as Determined by an IRC According to RECIST v1.1 in ITT Population

End point title	PFS as Determined by an IRC According to RECIST v1.1 in ITT Population

End point description:

PFS was defined as the time from randomization to PD, as determined by an IRC per RECIST v1.1, or death from any cause, whichever occurred first. PD: >/=20% relative increase and >/=5 mm of

absolute increase in the SoD of all TLs, taking as reference the smallest SoD recorded since treatment started; >/=1 new lesion(s); and/or unequivocal progression of non-TLs. Participants without PFS event were censored at the last tumor assessment date. Participants with no post-baseline tumor assessments were censored at the randomization date + 1 day. Median PFS was estimated by Kaplan-Meier method and 95% CI was assessed using the method of Brookmeyer and Crowley. Analysis was performed on the ITT Population.

End point type	Secondary

End point timeframe:

Baseline until documented PD or death, whichever occurred first (up to approximately 24 months)

End point values	Sunitinib	Atezolizumab + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	461	454		
Units: months				
median (confidence interval 95%)	8.3 (7.0 to 9.7)	9.6 (8.3 to 11.5)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Stratified Analysis: Strata were presence of liver metastases, Motzer score, PD-L1 level per interactive voice/web response system (IxRS).

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	915
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.1218
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	1.04

Notes:

[6] - Hazard ratio was estimated by Cox regression.

Secondary: Percentage of Participants with PD as Determined by an IRC According to RECIST v1.1 or Death from Any Cause in PD-L1-Selected Population

End point title	Percentage of Participants with PD as Determined by an IRC According to RECIST v1.1 or Death from Any Cause in PD-L1-Selected Population

End point description:

Tumor response was assessed by an IRC according to RECIST v1.1. PD was defined as >/=20% relative increase in the SoD of all TLs, taking as reference the smallest SoD on study, including baseline, and an absolute increase of >/=5 mm; >/=1 new lesion(s); and/or unequivocal progression of non-TLs. Analysis was performed on the PD-L1-Selected Population.

End point type	Secondary

End point timeframe:

Baseline until documented PD or death, whichever occurred first (until data cut-off date 29 September 2017, up to approximately 24 months)

End point values	Sunitinib	Atezolizumab + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184	178		
Units: percentage of participants				
number (not applicable)	64.7	62.9		

Statistical analyses

No statistical analyses for this end point

Secondary: PFS as Determined by an IRC According to RECIST v1.1 in PD-L1-Selected Population

End point title	PFS as Determined by an IRC According to RECIST v1.1 in PD-L1-Selected Population

End point description:

PFS was defined as the time from randomization to PD, as determined by an IRC per RECIST v1.1, or death from any cause, whichever occurred first. PD: >/=20% relative increase in the SoD of all TLs, taking as reference the smallest SoD on study, including baseline, and an absolute increase of >/=5 mm; >/=1 new lesion(s); and/or unequivocal progression of non-TLs. Participants without PFS event were censored at the last tumor assessment date. Participants with no post-baseline tumor assessments were censored at the randomization date + 1 day. Median PFS was estimated by Kaplan-Meier method and 95% CI was assessed using the method of Brookmeyer and Crowley. Analysis was performed on the PD-L1-Selected Population.

End point type	Secondary

End point timeframe:

Baseline until documented PD or death, whichever occurred first (until data cut-off date 29 September 2017, up to approximately 24 months)

End point values	Sunitinib	Atezolizumab + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184	178		
Units: months				
median (confidence interval 95%)	7.2 (6.1 to 11.1)	8.9 (6.9 to 12.5)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Stratified Analysis: Strata were presence of liver metastases, Motzer score, PD-L1 level per interactive voice/web response system (IxRS).

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	362
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.6138
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.21

Notes:

[7] - Hazard ratio was estimated by Cox regression.

Secondary: Percentage of Participants with an Objective Response of Complete Response (CR) or Partial Response (PR) as Determined by the Investigator According to RECIST v1.1 in Objective Response Rate (ORR)-Evaluable Population

End point title	Percentage of Participants with an Objective Response of Complete Response (CR) or Partial Response (PR) as Determined by the Investigator According to RECIST v1.1 in Objective Response Rate (ORR)-Evaluable Population

End point description:

Tumor response was assessed by the investigator according to RECIST v1.1. Objective response was defined as percentage of participants with a documented CR or PR. CR was defined as disappearance of all TLs/non-TLs and (if applicable) normalization of tumor marker level or reduction in short axis of any pathological lymph nodes to less than (<) 10 mm. PR was defined as >/=30% decrease in the SoD of TLs (taking as reference the baseline SoD) or persistence of >/=1 non-TL(s) and/or (if applicable) maintenance of tumor marker level above the normal limits. The 95% CI was computed using Clopper-Pearson approach. Participants without any post-baseline tumor assessments were considered non-responders. Analysis was performed on the ORR-Evaluable Population, which included all participants in the ITT population with measurable disease at baseline, as determined by the investigator.

End point type	Secondary

End point timeframe:

Baseline until documented CR/PR, PD, or death, whichever occurred first (until data cut-off date 29 September 2017, up to approximately 24 months)

End point values	Sunitinib	Atezolizumab + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	460	454		
Units: percentage of participants				
number (confidence interval 95%)	33.3 (28.97 to 37.77)	36.6 (32.12 to 41.18)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Stratified Analysis: Strata were presence of liver metastases, Motzer score, PD-L1 level per interactive voice/web response system (IxRS).

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	914
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.2733
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Response Rates
Point estimate	3.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.09
upper limit	9.7

Notes:

[8] - 95% CI for difference in response rates was constructed using Wald method.

Secondary: Duration of Response (DOR) as Determined by the Investigator According to RECIST v1.1 in DOR-Evaluable Population

End point title	Duration of Response (DOR) as Determined by the Investigator According to RECIST v1.1 in DOR-Evaluable Population

End point description:

DOR: the time from the first CR/PR to PD as determined by the investigator per RECIST v1.1 or death from any cause. CR: disappearance of TLs/non-TLs and normalization of tumor marker level or reduction in short axis of any pathological lymph nodes to <10 mm. PR: >/=30% decrease in the SoD of TLs or persistence of >/=1 non-TL(s) and/or maintenance of tumor marker level above the normal limits. PD: >/=20% relative increase in the SoD of all TLs, taking as reference the smallest SoD on study, including baseline, and an absolute increase of >/=5 mm; >/=1 new lesion(s); and/or unequivocal progression of non-TLs. Participants without PD or death after a CR/PR were censored at last tumor assessment. Participants without tumor assessments after a CR/PR were censored at first CR/PR + 1 day. Median DOR was estimated by Kaplan-Meier method and 95% CI by the method of Brookmeyer and Crowley. DOR-Evaluable Population: all participants with a CR/PR in the ORR-Evaluable Population.

End point type	Secondary

End point timeframe:

Baseline until documented CR/PR, PD, or death, whichever occurred first (until data cut-off date 29 September 2017, up to approximately 24 months)

End point values	Sunitinib	Atezolizumab + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153[9]	166[10]		
Units: months				
median (confidence interval 95%)	14.2 (11.3 to 99999)	16.6 (15.4 to 99999)		

Notes:

[9] - 99999 = Upper limit of 95% CI could not be estimated due to high number of censored participants.

[10] - 99999 = Upper limit of 95% CI could not be estimated due to high number of censored participants.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with an Objective Response of CR or PR as Determined by an IRC According to RECIST v1.1 in ORR-Evaluable Population

End point title	Percentage of Participants with an Objective Response of CR or PR as Determined by an IRC According to RECIST v1.1 in ORR-Evaluable Population

End point description:

Tumor response was assessed by an IRC according to RECIST v1.1. Objective response was defined as percentage of participants with a documented CR or PR. CR was defined as disappearance of all TLs/non-TLs and (if applicable) normalization of tumor marker level or reduction in short axis of any pathological lymph nodes to <10 mm. PR was defined as >/=30% decrease in the SoD of TLs (taking as reference the baseline SoD) or persistence of >/=1 non-TL(s) and/or (if applicable) maintenance of tumor marker level above the normal limits. The 95% CI was computed using Clopper-Pearson approach. Participants without any post-baseline tumor assessments were considered non-responders. Analysis was performed on the ORR-Evaluable Population.

End point type	Secondary

End point timeframe:

Baseline until documented CR/PR, PD, or death, whichever occurred first (until data cut-off date 29 September 2017, up to approximately 24 months)

End point values	Sunitinib	Atezolizumab + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	460	454		
Units: percentage of participants				
number (confidence interval 95%)	31.3 (27.09 to 35.76)	33.3 (28.94 to 37.80)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Stratified Analysis: Strata were presence of liver metastases, Motzer score, PD-L1 level per interactive voice/web response system (IxRS).

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab

Number of subjects included in analysis	914
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.5121
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Response Rates
Point estimate	1.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.32
upper limit	8.24

Notes:

[11] - 95% CI for difference in response rates was constructed using Wald method.

Secondary: DOR as Determined by an IRC According to RECIST v1.1 in DOR-Evaluable Population

End point title	DOR as Determined by an IRC According to RECIST v1.1 in DOR-Evaluable Population

End point description:

DOR was defined as the time from the first occurrence of CR/PR to PD as determined by an IRC per RECIST v1.1, or death from any cause, whichever occurred first. CR: disappearance of TLs/non-TLs and normalization of tumor marker level or reduction in short axis of any pathological lymph nodes to <10 mm. PR: >/=30% decrease in the SoD of TLs or persistence of >/=1 non-TL(s) and/or maintenance of tumor marker level above the normal limits. PD: >/=20% relative increase in the SoD of all TLs, taking as reference the smallest SoD on study, including baseline, and an absolute increase of >/=5 mm; >/=1 new lesion(s); and/or unequivocal progression of non-TLs. Participants without PD or death after a CR/PR were censored at last tumor assessment. Participants without tumor assessments after a CR/PR were censored at first CR/PR + 1 day. Median DOR was estimated by Kaplan-Meier method and 95% CI by the method of Brookmeyer and Crowley. Analysis was performed on the DOR-Evaluable Population.

End point type	Secondary

End point timeframe:

Baseline until documented CR/PR, PD, or death, whichever occurred first (until data cut-off date 29 September 2017, up to approximately 24 months)

End point values	Sunitinib	Atezolizumab + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144[12]	151[13]		
Units: months				
median (confidence interval 95%)	18.6 (13.8 to 99999)	99999 (16.8 to 99999)		

Notes:

[12] - 99999 = Upper limit of 95% CI could not be estimated due to high number of censored participants.
[13] - 99999=Median/Upper limit of CI could not be estimated due to high number of censored participants.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with PD as Determined by the Investigator

According to Immune-Modified RECIST or Death from Any Cause in ITT Population

End point title	Percentage of Participants with PD as Determined by the Investigator According to Immune-Modified RECIST or Death from Any Cause in ITT Population

End point description:

Tumor response was assessed by the investigator according to immune-modified RECIST. PD was defined as >/=20% relative increase in the SoD of all TLs and all new measurable lesions, taking as reference the smallest SoD on study, including baseline, and an absolute increase of >/=5 mm. Analysis was performed on the ITT Population.

End point type	Secondary

End point timeframe:

Baseline until documented PD or death, whichever occurred first (until data cut-off date 29 September 2017, up to approximately 24 months)

End point values	Sunitinib	Atezolizumab + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	461	454		
Units: percentage of participants				
number (not applicable)	58.1	55.1		

Statistical analyses

No statistical analyses for this end point

Secondary: PFS as Determined by the Investigator According to Immune-Modified RECIST in ITT Population

End point title	PFS as Determined by the Investigator According to Immune-Modified RECIST in ITT Population

End point description:

PFS was defined as the time from randomization to PD, as determined by the investigator per immune-modified RECIST or death from any cause, whichever occurred first. PD: >/=20% relative increase in the SoD of all TLs and all new measurable lesions, taking as reference the smallest SoD on study, including baseline, and an absolute increase of >/=5 mm. Participants without PFS event were censored at the last tumor assessment date. Participants with no post-baseline tumor assessments were censored at the randomization date + 1 day. Median PFS was estimated by Kaplan-Meier method and 95% CI was assessed using the method of Brookmeyer and Crowley. Analysis was performed on the ITT Population.

End point type	Secondary

End point timeframe:

Baseline until documented PD or death, whichever occurred first (until data cut-off date 29 September 2017, up to approximately 24 months)

End point values	Sunitinib	Atezolizumab + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	461	454		
Units: months				
median (confidence interval 95%)	12.3 (9.8 to 13.7)	13.9 (12.5 to 15.3)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Stratified Analysis: Strata were presence of liver metastases, Motzer score, PD-L1 level per interactive voice/web response system (IxRS).

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	915
Analysis specification	Pre-specified
Analysis type	superiority[14]
P-value	= 0.0606
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.01

Notes:

[14] - Hazard ratio was estimated by Cox regression.

Secondary: Percentage of Participants with an Objective Response of CR or PR as Determined by the Investigator According to Immune-Modified RECIST in ORR-Evaluable Population

End point title	Percentage of Participants with an Objective Response of CR or PR as Determined by the Investigator According to Immune-Modified RECIST in ORR-Evaluable Population

End point description:

Tumor response was assessed by the investigator according to immune-modified RECIST. Objective response was defined as percentage of participants with a documented CR or PR. CR was defined as disappearance of all TLs/non-TLs or reduction in short axis of any pathological lymph nodes to <10 mm. PR was defined as >/=30% decrease in the SoD of TLs and all new measurable lesions (taking as reference the baseline SoD), in the absence of CR. The 95% CI was computed using Clopper-Pearson approach. Participants without any post-baseline tumor assessments were considered non-responders. Analysis was performed on the ORR-Evaluable Population.

End point type	Secondary

End point timeframe:

Baseline until documented CR/PR, PD, or death, whichever occurred first (until data cut-off date 29 September 2017, up to approximately 24 months)

End point values	Sunitinib	Atezolizumab + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	460	454		
Units: percentage of participants				
number (confidence interval 95%)	35.0 (30.64 to 39.55)	40.1 (35.55 to 44.76)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Stratified Analysis: Strata were presence of liver metastases, Motzer score, PD-L1 level per interactive voice/web response system (IxRS).

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	914
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	= 0.1011
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Response Rates
Point estimate	5.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	11.58

Notes:

[15] - 95% CI for difference in response rates was constructed using Wald method.

Secondary: DOR as Determined by the Investigator According to Immune-Modified RECIST in DOR-Evaluable Population

End point title	DOR as Determined by the Investigator According to Immune-Modified RECIST in DOR-Evaluable Population

End point description:

DOR was defined as the time from the first occurrence of CR/PR to PD as determined by the investigator per immune-modified RECIST or death from any cause, whichever occurred first. CR: disappearance of TLs/non-TLs or reduction in short axis of any pathological lymph nodes to <10 mm. PR: >/=30% decrease in the SoD of TLs and all new measurable lesions (taking as reference the baseline SoD), in the absence of CR. PD: >/=20% relative increase in the SoD of all TLs and all new measurable lesions, taking as reference the smallest SoD on study, including baseline, and an absolute increase of >/=5 mm. Participants without PD or death after a CR/PR were censored at last tumor assessment. Participants without tumor assessments after a CR/PR were censored at first CR/PR + 1 day. Median DOR was estimated by Kaplan-Meier method and 95% CI by the method of Brookmeyer and Crowley. Analysis was performed on DOR-evaluable population.

End point type	Secondary

End point timeframe:

Baseline until documented CR/PR, PD, or death, whichever occurred first (until data cut-off date 29 September 2017, up to approximately 24 months)

End point values	Sunitinib	Atezolizumab + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161	182[16]		
Units: months				
median (confidence interval 95%)	19.4 (13.1 to 20.0)	19.4 (16.5 to 99999)		

Notes:

[16] - 99999 = Upper limit of 95% CI could not be estimated due to high number of censored participants.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with PD as Determined by the Investigator According to RECIST v1.1 or Death from Any Cause in ITT Population

End point title	Percentage of Participants with PD as Determined by the Investigator According to RECIST v1.1 or Death from Any Cause in ITT Population

End point description:

Tumor response was assessed by the investigator according to RECIST v1.1. PD was defined as >/=20% relative increase in the SoD of all TLs, taking as reference the smallest SoD on study, including baseline, and an absolute increase of >/=5 mm; >/=1 new lesion(s); and/or unequivocal progression of non-TLs. Analysis was performed on the ITT Population.

End point type	Secondary

End point timeframe:

Baseline until documented PD or death, whichever occurred first (until data cut-off date 29 September 2017, up to approximately 24 months)

End point values	Sunitinib	Atezolizumab + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	461	454		
Units: percentage of participants				
number (not applicable)	63.8	60.1		

Statistical analyses

No statistical analyses for this end point

Secondary: PFS as Determined by the Investigator According to RECIST v1.1 in ITT Population

End point title	PFS as Determined by the Investigator According to RECIST v1.1 in ITT Population

End point description:

PFS was defined as the time from randomization to PD, as determined by the investigator per RECIST v1.1 or death from any cause, whichever occurred first. PD: >/=20% relative increase in the SoD of all TLs, taking as reference the smallest SoD on study, including baseline, and an absolute increase of >/=5 mm; >/=1 new lesion(s); and/or unequivocal progression of non-TLs. Participants without PFS event were censored at the last tumor assessment date. Participants with no post-baseline tumor assessments were censored at the randomization date + 1 day. Participants with a PFS event who

missed >/=2 scheduled assessments immediately prior to the PFS event were censored at the last tumor assessment prior to the missed visits. Median PFS was estimated by Kaplan-Meier method and 95% CI was assessed using the method of Brookmeyer and Crowley. Analysis was performed on the ITT Population.

End point type	Secondary

End point timeframe:

Baseline until documented PD or death, whichever occurred first (until data cut-off date 29 September 2017, up to approximately 24 months)

End point values	Sunitinib	Atezolizumab + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	461	454		
Units: months				
median (confidence interval 95%)	8.4 (7.5 to 9.7)	11.2 (9.6 to 13.6)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Stratified Analysis: Strata were presence of liver metastases, Motzer score, PD-L1 level per interactive voice/web response system (IxRS).

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	915
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	= 0.0254
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	0.98

Notes:

[17] - Hazard ratio was estimated by Cox regression.

Secondary: Percentage of Participants with PD as Determined by the Investigator According to RECIST v1.1 or Death from Any Cause in Participants with Sarcomatoid Histology

End point title	Percentage of Participants with PD as Determined by the Investigator According to RECIST v1.1 or Death from Any Cause in Participants with Sarcomatoid Histology

End point description:

Tumor response was assessed by the investigator according to RECIST v1.1. PD was defined as >/=20% relative increase in the SoD of all TLs, taking as reference the smallest SoD on study, including baseline, and an absolute increase of >/=5 mm; >/=1 new lesion(s); and/or unequivocal progression of non-TLs. Analysis was performed on the ITT Population participants with sarcomatoid histology (defined

by investigator-assessed conventional histopathology).

End point type	Secondary

End point timeframe:

Baseline until documented PD or death, whichever occurred first (until data cut-off date 29 September 2017, up to approximately 24 months)

End point values	Sunitinib	Atezolizumab + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	68		
Units: percentage of participants				
number (not applicable)	85.1	67.6		

Statistical analyses

No statistical analyses for this end point

Secondary: PFS as Determined by the Investigator According to RECIST v1.1 in Participants with Sarcomatoid Histology

End point title	PFS as Determined by the Investigator According to RECIST v1.1 in Participants with Sarcomatoid Histology

End point description:

PFS was defined as the time from randomization to PD, as determined by the investigator per RECIST v1.1 or death from any cause, whichever occurred first. PD: >/=20% relative increase in the SoD of all TLs, taking as reference the smallest SoD on study, including baseline, and an absolute increase of >/=5 mm; >/=1 new lesion(s); and/or unequivocal progression of non-TLs. Participants without PFS event were censored at the last tumor assessment date. Participants with no post-baseline tumor assessments were censored at the randomization date + 1 day. Median PFS was estimated by Kaplan-Meier method and 95% CI was assessed using the method of Brookmeyer and Crowley. Analysis was performed on the ITT Population participants with sarcomatoid histology.

End point type	Secondary

End point timeframe:

Baseline until documented PD or death, whichever occurred first (until data cut-off date 29 September 2017, up to approximately 24 months)

End point values	Sunitinib	Atezolizumab + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	68		
Units: months				
median (confidence interval 95%)	5.3 (3.3 to 6.7)	8.3 (5.4 to 12.9)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Stratified Analysis: Strata were presence of liver metastases, Motzer score, PD-L1 level per interactive voice/web response system (IxRS).

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority[18]
P-value	= 0.002
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	0.79

Notes:

[18] - Hazard ratio was estimated by Cox regression.

Secondary: Percentage of Participants Who Died of Any Cause in Participants with Sarcomatoid Histology

End point title	Percentage of Participants Who Died of Any Cause in Participants with Sarcomatoid Histology

End point description:

Percentage of participants who died of any cause was reported. Analysis was performed on the ITT Population participants with sarcomatoid histology.

End point type	Secondary

End point timeframe:

Baseline until death from any cause (until data cut-off date 29 September 2017, up to approximately 27 months)

End point values	Sunitinib	Atezolizumab + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	68		
Units: percentage of participants				
number (not applicable)	50.0	38.2		

Statistical analyses

No statistical analyses for this end point

Secondary: OS in Participants with Sarcomatoid Histology

End point title	OS in Participants with Sarcomatoid Histology

End point description:

OS was defined as the time from randomization to death due to any cause. Participants who were not

reported as having died at the date of analysis were censored at the date when they were last known to be alive. Participants who did not have post-baseline information were censored at the date of randomization + 1 day. Median OS was estimated by Kaplan-Meier method and 95% CI was assessed using the method of Brookmeyer and Crowley. Analysis was performed on the ITT Population participants with sarcomatoid histology. The data '99999' in the results signifies that median and/or upper limit of 95% CI could not be estimated due to high number of censored participants.

End point type	Secondary

End point timeframe:

Baseline until death from any cause (until data cut-off date 29 September 2017, up to approximately 27 months)

End point values	Sunitinib	Atezolizumab + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	68		
Units: months				
median (confidence interval 95%)	15.0 (8.7 to 99999)	99999 (18.3 to 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Stratified Analysis: Strata were presence of liver metastases, Motzer score, PD-L1 level per interactive voice/web response system (IxRS).

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	= 0.0323
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.32
upper limit	0.96

Notes:

[19] - Hazard ratio was estimated by Cox regression.

Secondary: Change from Baseline in Symptom Interference as Determined by M.D. Anderson Symptom Inventory (MDASI) Part II Score

End point title	Change from Baseline in Symptom Interference as Determined by M.D. Anderson Symptom Inventory (MDASI) Part II Score

End point description:

The MDASI is a self-report questionnaire that comprises of 23 items and two subscales: symptom severity (17 items) and symptom interference (6 items). In Part II, participants were asked to rate how much the symptoms have interfered with 6 areas of function (general activity, walking, work, mood, relations with other people, and enjoyment of life) in the last 24 hours. Each item was rated on a scale

of 0 (does not interfere) to 10 (interfered completely) and total Part II score was calculated as an average of 6-item scores. Repeated measures model-estimated least-squares (LS) mean score for changes from baseline is reported at each timepoint, where a negative value indicates improvement. Analysis was performed on the patient-reported outcome (PRO)-Evaluable Population, which included all participants with a non-missing baseline PRO assessment and >/=1 post-baseline PRO assessment. Here, 'n'= number of participants evaluable at specified time point for different arms, respectively.

End point type	Secondary

End point timeframe:

Baseline (Day 1 Cycle 1); Day 22 Cycle 1; Day 1 and 22 of every cycle from Cycle 2 up to Cycle 19; Cycle length = 42 days

End point values	Sunitinib	Atezolizumab + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	359[20]	373		
Units: units on a scale				
least squares mean (standard error)				
Change at Cycle1 Day 22 (n=260,301)	1.28 (± 0.13)	0.54 (± 0.13)		
Change at Cycle 2 Day 1 (n=276,305)	0.76 (± 0.13)	0.56 (± 0.13)		
Change at Cycle 2 Day 22 (n=248,284)	1.58 (± 0.13)	0.56 (± 0.13)		
Change at Cycle 3 Day 1 (n=253,297)	1.05 (± 0.13)	0.53 (± 0.13)		
Change at Cycle 3 Day 22 (n=226,279)	1.63 (± 0.14)	0.61 (± 0.13)		
Change at Cycle 4 Day 1 (n=230,266)	1.02 (± 0.14)	0.59 (± 0.13)		
Change at Cycle 4 Day 22 (n=217,252)	1.55 (± 0.14)	0.57 (± 0.14)		
Change at Cycle 5 Day 1 (n=211,238)	1.18 (± 0.15)	0.72 (± 0.14)		
Change at Cycle 5 Day 22 (n=196,238)	1.56 (± 0.15)	0.78 (± 0.14)		
Change at Cycle 6 Day 1 (n=198,224)	1.03 (± 0.15)	0.82 (± 0.14)		
Change at Cycle 6 Day 22 (n=183,207)	1.44 (± 0.15)	0.80 (± 0.15)		
Change at Cycle 7 Day 1 (n=173,200)	1.15 (± 0.16)	0.72 (± 0.15)		
Change at Cycle 7 Day 22 (n=163,191)	1.43 (± 0.16)	0.66 (± 0.15)		
Change at Cycle 8 Day 1 (n=161,192)	1.06 (± 0.16)	0.76 (± 0.15)		
Change at Cycle 8 Day 22 (n=150,186)	1.34 (± 0.17)	0.69 (± 0.15)		
Change at Cycle 9 Day 1 (n=146,185)	1.05 (± 0.17)	0.67 (± 0.16)		
Change at Cycle 9 Day 22 (n=135,172)	1.46 (± 0.18)	0.56 (± 0.16)		
Change at Cycle 10 Day 1 (n=131,169)	1.24 (± 0.18)	0.61 (± 0.16)		
Change at Cycle 10 Day 22 (n=78,151)	1.61 (± 0.20)	0.60 (± 0.17)		
Change at Cycle 11 Day 1 (n=100,134)	1.12 (± 0.19)	0.62 (± 0.17)		
Change at Cycle 11 Day 22 (n=59,122)	1.45 (± 0.21)	0.61 (± 0.18)		
Change at Cycle 12 Day 1 (n=73,110)	1.02 (± 0.21)	0.53 (± 0.18)		
Change at Cycle 12 Day 22 (n=47,93)	1.45 (± 0.24)	0.69 (± 0.20)		
Change at Cycle 13 Day 1 (n=52,81)	0.79 (± 0.24)	0.80 (± 0.21)		
Change at Cycle 13 Day 22 (n=36,72)	1.09 (± 0.27)	0.73 (± 0.22)		
Change at Cycle 14 Day 1 (n=39,57)	0.86 (± 0.27)	0.73 (± 0.24)		
Change at Cycle 14 Day 22 (n=27,54)	1.22 (± 0.31)	0.83 (± 0.25)		
Change at Cycle 15 Day 1 (n=31,43)	0.93 (± 0.31)	0.78 (± 0.27)		
Change at Cycle 15 Day 22 (n=17,36)	1.67 (± 0.37)	0.88 (± 0.29)		
Change at Cycle 16 Day 1 (n=20,27)	0.90 (± 0.38)	0.98 (± 0.32)		
Change at Cycle 16 Day 22 (n=13,22)	1.30 (± 0.43)	1.32 (± 0.36)		
Change at Cycle 17 Day 1 (n=13,19)	0.80 (± 0.46)	1.18 (± 0.40)		
Change at Cycle 17 Day 22 (n=9,11)	0.92 (± 0.53)	0.95 (± 0.47)		
Change at Cycle 18 Day 1 (n=6,9)	0.75 (± 0.64)	0.75 (± 0.53)		

Change at Cycle 18 Day 22 (n=3,6)	0.65 (± 0.86)	0.87 (± 0.63)		
Change at Cycle 19 Day 1 (n=1,5)	0.29 (± 1.58)	0.80 (± 0.73)		
Change at Cycle 19 Day 22 (n=0,2)	99999 (± 99999)	0.88 (± 1.03)		

Notes:

[20] - '99999' = data not available as no participant was evaluable at specified time point.

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Cycle 1 Day 22 (Actual number of participants included in the analysis = 561): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[21]
P-value	< 0.0001
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	-0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.06
upper limit	-0.43

Notes:

[21] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Cycle 2 Day 1 (Actual number of participants included in the analysis = 581): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[22]
P-value	= 0.2085
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.51
upper limit	0.11

Notes:

[22] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Cycle 2 Day 22 (Actual number of participants included in the analysis = 532): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[23]
P-value	< 0.0001
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	-1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.33
upper limit	-0.71

Notes:

[23] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

Cycle 3 Day 1 (Actual number of participants included in the analysis = 550): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[24]
P-value	= 0.0013
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	-0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.82
upper limit	-0.2

Notes:

[24] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 5

Statistical analysis description:

Cycle 3 Day 22 (Actual number of participants included in the analysis = 505): Repeated measures

model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[25]
P-value	< 0.0001
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	-1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.34
upper limit	-0.7

Notes:

[25] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 6

Statistical analysis description:

Cycle 4 Day 1 (Actual number of participants included in the analysis = 496): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[26]
P-value	= 0.0098
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	-0.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.76
upper limit	-0.1

Notes:

[26] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 7

Statistical analysis description:

Cycle 4 Day 22 (Actual number of participants included in the analysis = 469): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab

Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[27]
P-value	< 0.0001
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	-0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.32
upper limit	-0.65

Notes:

[27] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 8

Statistical analysis description:

Cycle 5 Day 1 (Actual number of participants included in the analysis = 449): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[28]
P-value	= 0.008
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	-0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	-0.12

Notes:

[28] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 9

Statistical analysis description:

Cycle 5 Day 22 (Actual number of participants included in the analysis = 434): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[29]
P-value	< 0.0001
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	-0.78

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.13
upper limit	-0.44

Notes:

[29] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 10

Statistical analysis description:

Cycle 6 Day 1 (Actual number of participants included in the analysis = 422): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[30]
P-value	= 0.2512
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	-0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.56
upper limit	0.15

Notes:

[30] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 11

Statistical analysis description:

Cycle 6 Day 22 (Actual number of participants included in the analysis = 390): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[31]
P-value	= 0.0005
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	-0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.01
upper limit	-0.28

Notes:

[31] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 12

Statistical analysis description:

Cycle 7 Day 1 (Actual number of participants included in the analysis = 373): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[32]
P-value	= 0.0247
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	-0.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	-0.05

Notes:

[32] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 13

Statistical analysis description:

Cycle 7 Day 22 (Actual number of participants included in the analysis = 354): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[33]
P-value	< 0.0001
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	-0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.15
upper limit	-0.39

Notes:

[33] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 14

Statistical analysis description:

Cycle 8 Day 1 (Actual number of participants included in the analysis = 353): Repeated measures

model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[34]
P-value	= 0.1411
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	-0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.68
upper limit	0.1

Notes:

[34] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 15

Statistical analysis description:

Cycle 8 Day 22 (Actual number of participants included in the analysis = 336): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[35]
P-value	= 0.0014
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	-0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.05
upper limit	-0.25

Notes:

[35] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 16

Statistical analysis description:

Cycle 9 Day 1 (Actual number of participants included in the analysis = 331): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab

Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[36]
P-value	= 0.0728
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	-0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.78
upper limit	0.03

Notes:

[36] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 17

Statistical analysis description:

Cycle 9 Day 22 (Actual number of participants included in the analysis = 307): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[37]
P-value	< 0.0001
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.32
upper limit	-0.49

Notes:

[37] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 18

Statistical analysis description:

Cycle 10 Day 1 (Actual number of participants included in the analysis = 300): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[38]
P-value	= 0.0041
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	-0.62

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.05
upper limit	-0.2

Notes:

[38] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 19

Statistical analysis description:

Cycle 10 Day 22 (Actual number of participants included in the analysis = 229): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[39]
P-value	< 0.0001
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.46
upper limit	-0.55

Notes:

[39] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 20

Statistical analysis description:

Cycle 11 Day 1 (Actual number of participants included in the analysis = 234): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[40]
P-value	= 0.0353
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.96
upper limit	-0.03

Notes:

[40] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 21

Statistical analysis description:

Cycle 11 Day 22 (Actual number of participants included in the analysis = 181): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[41]
P-value	= 0.0011
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	-0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.35
upper limit	-0.34

Notes:

[41] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 22

Statistical analysis description:

Cycle 12 Day 1 (Actual number of participants included in the analysis = 183): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[42]
P-value	= 0.0582
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.01
upper limit	0.02

Notes:

[42] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 23

Statistical analysis description:

Cycle 12 Day 22 (Actual number of participants included in the analysis = 140): Repeated measures

model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[43]
P-value	= 0.0089
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	-0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.32
upper limit	-0.19

Notes:

[43] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 24

Statistical analysis description:

Cycle 13 Day 1 (Actual number of participants included in the analysis = 133): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[44]
P-value	= 0.9575
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.57
upper limit	0.61

Notes:

[44] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 25

Statistical analysis description:

Cycle 13 Day 22 (Actual number of participants included in the analysis = 108): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab

Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[45]
P-value	= 0.2745
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	-0.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.01
upper limit	0.29

Notes:

[45] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 26

Statistical analysis description:

Cycle 14 Day 1 (Actual number of participants included in the analysis = 96): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[46]
P-value	= 0.7088
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	-0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.81
upper limit	0.55

Notes:

[46] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 27

Statistical analysis description:

Cycle 14 Day 22 (Actual number of participants included in the analysis = 81): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[47]
P-value	= 0.3077
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	-0.39

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.13
upper limit	0.36

Notes:

[47] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 28

Statistical analysis description:

Cycle 15 Day 1 (Actual number of participants included in the analysis = 74): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[48]
P-value	= 0.7112
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.93
upper limit	0.63

Notes:

[48] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 29

Statistical analysis description:

Cycle 15 Day 22 (Actual number of participants included in the analysis = 53): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[49]
P-value	= 0.0837
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	-0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.69
upper limit	0.11

Notes:

[49] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 30

Statistical analysis description:

Cycle 16 Day 1 (Actual number of participants included in the analysis = 47): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[50]
P-value	= 0.8655
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.88
upper limit	1.04

Notes:

[50] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 31

Statistical analysis description:

Cycle 16 Day 22 (Actual number of participants included in the analysis = 35): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[51]
P-value	= 0.9725
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.07
upper limit	1.11

Notes:

[51] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 32

Statistical analysis description:

Cycle 17 Day 1 (Actual number of participants included in the analysis = 32): Repeated measures

model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[52]
P-value	= 0.5285
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	0.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	1.55

Notes:

[52] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 33

Statistical analysis description:

Cycle 17 Day 22 (Actual number of participants included in the analysis = 20): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[53]
P-value	= 0.9663
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.34
upper limit	1.4

Notes:

[53] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 34

Statistical analysis description:

Cycle 18 Day 1 (Actual number of participants included in the analysis = 15): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab

Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[54]
P-value	= 0.9914
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.61
upper limit	1.63

Notes:

[54] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 35

Statistical analysis description:

Cycle 18 Day 22 (Actual number of participants included in the analysis = 9): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[55]
P-value	= 0.8345
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.85
upper limit	2.3

Notes:

[55] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 36

Statistical analysis description:

Cycle 19 Day 1 (Actual number of participants included in the analysis = 6): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[56]
P-value	= 0.7725
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	0.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.9
upper limit	3.91

Notes:

[56] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Secondary: Change from Baseline in Symptom Severity as Determined by MDASI Part I Score

End point title	Change from Baseline in Symptom Severity as Determined by MDASI Part I Score

End point description:

The MDASI is a cancer-related, multi-symptom, valid, and reliable self-report questionnaire that comprises of 23 items and two subscales: symptom severity (17 items) and symptom interference (6 items). In Part I, participants were asked to rate how severe the symptoms (pain, fatigue, nausea, disturbed sleep, feeling of being distressed, shortness of breath, remembering things, lack of appetite, drowsy, dry mouth, feeling sad, vomiting, numbness or tingling, rash/skin changes, headache, mouth/throat sores, and diarrhea) were when "at their worst" in the last 24 hours. Each item was rated on a scale of 0 (not present) to 10 (as bad as you can imagine). Mixed-effects model-estimated LS mean score for change from baseline at the end-of-treatment is reported for each item, where a negative value indicates improvement. Analysis was performed on the PRO-Evaluable Population. Here, 'Number of Subject Analysed' = number of participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline; End of Treatment (EoT) visit (up to approximately 27 months)

End point values	Sunitinib	Atezolizumab + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	337	358		
Units: units on a scale				
least squares mean (standard error)				
Pain: Change at EoT	1.41 (± 0.15)	0.92 (± 0.15)		
Fatigue: Change at EoT	1.83 (± 0.15)	1.20 (± 0.15)		
Nausea: Change at EoT	1.20 (± 0.11)	0.29 (± 0.11)		
Disturbed sleep: Change at EoT	0.71 (± 0.14)	0.19 (± 0.14)		
Feeling of Being distressed: Change at EoT	0.82 (± 0.14)	0.25 (± 0.14)		
Shortness of breath: Change at EoT	1.15 (± 0.13)	0.58 (± 0.13)		
Remembering things: Change at EoT	0.93 (± 0.12)	0.60 (± 0.11)		
Lack of appetite: Change at EoT	1.59 (± 0.14)	0.40 (± 0.14)		
Drowsy: Change at EoT	1.32 (± 0.14)	0.79 (± 0.14)		
Dry mouth: Change at EoT	1.67 (± 0.15)	0.67 (± 0.15)		
Feeling sad: Change at EoT	0.88 (± 0.14)	0.28 (± 0.14)		
Vomiting: Change at EoT	0.66 (± 0.09)	0.08 (± 0.09)		
Numbness or tingling: Change at EoT	1.01 (± 0.12)	0.67 (± 0.12)		
Rash/skin changes: Change at EoT	2.08 (± 0.13)	1.00 (± 0.13)		
Headache: Change at EoT	0.70 (± 0.11)	0.66 (± 0.11)		
Mouth/throat sores: Change at EoT	1.76 (± 0.13)	0.74 (± 0.13)		
Diarrhea: Change at EoT	1.37 (± 0.10)	0.29 (± 0.10)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Pain: Mixed-effects model, assuming unstructured covariance matrix, with a term for treatment group, a term for visit time as a continuous variable, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model. The random effects are intercept and slope of visit time.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	695
Analysis specification	Pre-specified
Analysis type	superiority[57]
P-value	= 0.001
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.77
upper limit	-0.2

Notes:

[57] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Fatigue: Mixed-effects model, assuming unstructured covariance matrix, with a term for treatment group, a term for visit time as a continuous variable, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model. The random effects are intercept and slope of visit time.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	695
Analysis specification	Pre-specified
Analysis type	superiority[58]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.91
upper limit	-0.34

Notes:

[58] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Nausea: Mixed-effects model, assuming unstructured covariance matrix, with a term for treatment group, a term for visit time as a continuous variable, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model. The random effects are intercept and slope of visit time.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	695
Analysis specification	Pre-specified
Analysis type	superiority[59]
P-value	< 0.0001
Method	Mixed Models Analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.13
upper limit	-0.69

Notes:

[59] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

Disturbed sleep: Mixed-effects model, assuming unstructured covariance matrix, with a term for treatment group, a term for visit time as a continuous variable, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model. The random effects are intercept and slope of visit time.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	695
Analysis specification	Pre-specified
Analysis type	superiority[60]
P-value	= 0.0002
Method	Mixed Models Analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.79
upper limit	-0.25

Notes:

[60] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 5

Statistical analysis description:

Being distressed: Mixed-effects model, assuming unstructured covariance matrix, with a term for treatment group, a term for visit time as a continuous variable, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model. The random effects are intercept and slope of visit time.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab

Number of subjects included in analysis	695
Analysis specification	Pre-specified
Analysis type	superiority[61]
P-value	< 0.0001
Method	Mixed Models Analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.84
upper limit	-0.29

Notes:

[61] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 6

Statistical analysis description:

Shortness of breath: Mixed-effects model, assuming unstructured covariance matrix, with a term for treatment group, a term for visit time as a continuous variable, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model. The random effects are intercept and slope of visit time.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	695
Analysis specification	Pre-specified
Analysis type	superiority[62]
P-value	< 0.0001
Method	Mixed Models Analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.81
upper limit	-0.32

Notes:

[62] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 7

Statistical analysis description:

Remembering things: Mixed-effects model, assuming unstructured covariance matrix, with a term for treatment group, a term for visit time as a continuous variable, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model. The random effects are intercept and slope of visit time.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	695
Analysis specification	Pre-specified
Analysis type	superiority[63]
P-value	= 0.0036
Method	Mixed Models Analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.33

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.56
upper limit	-0.11

Notes:

[63] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 8

Statistical analysis description:

Lack of appetite: Mixed-effects model, assuming unstructured covariance matrix, with a term for treatment group, a term for visit time as a continuous variable, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model. The random effects are intercept and slope of visit time.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	695
Analysis specification	Pre-specified
Analysis type	superiority[64]
P-value	< 0.0001
Method	Mixed Models Analysis
Parameter estimate	LS Mean Difference
Point estimate	-1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.46
upper limit	-0.91

Notes:

[64] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 9

Statistical analysis description:

Drowsy: Mixed-effects model, assuming unstructured covariance matrix, with a term for treatment group, a term for visit time as a continuous variable, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model. The random effects are intercept and slope of visit time.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	695
Analysis specification	Pre-specified
Analysis type	superiority[65]
P-value	= 0.0001
Method	Mixed Models Analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.81
upper limit	-0.27

Notes:

[65] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 10

Statistical analysis description:

Dry mouth: Mixed-effects model, assuming unstructured covariance matrix, with a term for treatment group, a term for visit time as a continuous variable, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model. The random effects are intercept and slope of visit time.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	695
Analysis specification	Pre-specified
Analysis type	superiority[66]
P-value	< 0.0001
Method	Mixed Models Analysis
Parameter estimate	LS Mean Difference
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.28
upper limit	-0.71

Notes:

[66] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 11

Statistical analysis description:

Feeling sad: Mixed-effects model, assuming unstructured covariance matrix, with a term for treatment group, a term for visit time as a continuous variable, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model. The random effects are intercept and slope of visit time.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	695
Analysis specification	Pre-specified
Analysis type	superiority[67]
P-value	< 0.0001
Method	Mixed Models Analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.87
upper limit	-0.33

Notes:

[67] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 12

Statistical analysis description:

Vomiting: Mixed-effects model, assuming unstructured covariance matrix, with a term for treatment group, a term for visit time as a continuous variable, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model. The random effects are intercept and slope of visit time.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab

Number of subjects included in analysis	695
Analysis specification	Pre-specified
Analysis type	superiority[68]
P-value	< 0.0001
Method	Mixed Models Analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.75
upper limit	-0.41

Notes:

[68] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 13

Statistical analysis description:

Numbness or tingling: Mixed-effects model, assuming unstructured covariance matrix, with a term for treatment group, a term for visit time as a continuous variable, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model. The random effects are intercept and slope of visit time.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	695
Analysis specification	Pre-specified
Analysis type	superiority[69]
P-value	= 0.0051
Method	Mixed Models Analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.58
upper limit	-0.1

Notes:

[69] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 14

Statistical analysis description:

Rash/Skin Changes: Mixed-effects model, assuming unstructured covariance matrix, with a term for treatment group, a term for visit time as a continuous variable, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model. The random effects are intercept and slope of visit time.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	695
Analysis specification	Pre-specified
Analysis type	superiority[70]
P-value	< 0.0001
Method	Mixed Models Analysis
Parameter estimate	LS Mean Difference
Point estimate	-1.08

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.33
upper limit	-0.83

Notes:

[70] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 15

Statistical analysis description:

Headache: Mixed-effects model, assuming unstructured covariance matrix, with a term for treatment group, a term for visit time as a continuous variable, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model. The random effects are intercept and slope of visit time.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	695
Analysis specification	Pre-specified
Analysis type	superiority[71]
P-value	= 0.6541
Method	Mixed Models Analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.26
upper limit	0.16

Notes:

[71] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 16

Statistical analysis description:

Mouth/Throat Sores: Mixed-effects model, assuming unstructured covariance matrix, with a term for treatment group, a term for visit time as a continuous variable, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model. The random effects are intercept and slope of visit time.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	695
Analysis specification	Pre-specified
Analysis type	superiority[72]
P-value	< 0.0001
Method	Mixed Models Analysis
Parameter estimate	LS Mean Difference
Point estimate	-1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.28
upper limit	-0.76

Notes:

[72] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 17

Statistical analysis description:

Diarrhea: Mixed-effects model, assuming unstructured covariance matrix, with a term for treatment group, a term for visit time as a continuous variable, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model. The random effects are intercept and slope of visit time.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	695
Analysis specification	Pre-specified
Analysis type	superiority[73]
P-value	< 0.0001
Method	Mixed Models Analysis
Parameter estimate	LS Mean Difference
Point estimate	-1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.27
upper limit	-0.88

Notes:

[73] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Secondary: Change from Baseline in Symptom Severity as Determined by Brief Fatigue Inventory (BFI) Interference Scale Score

End point title	Change from Baseline in Symptom Severity as Determined by Brief Fatigue Inventory (BFI) Interference Scale Score

End point description:

The BFI is a valid and reliable self-report questionnaire used to assess the severity and impact of cancer-related fatigue. BFI interference subscale (6 items) assessed the impact of fatigue on global domains (general activity, mood, walking ability, normal work, relations with other people, and enjoyment of life) in the last 24 hours. Each item was rated on a scale of 0 (does not interfere) to 10 (interfered completely). Change from baseline in the mean score of all 6 items at each timepoint is reported, where a negative value indicates improvement. Analysis was performed on the PRO-Evaluable Population. Here, 'Number of Subject Analysed' = number of participants evaluable for this outcome measure; 'n'= number of participants evaluable at specified time point for different arms, respectively; '9999' = data not available as no participant was evaluable at specified time point; and '99999' = Standard Deviation (SD) could not be estimated as only 1 participant was evaluable.

End point type	Secondary

End point timeframe:

Baseline (Day 1 Cycle 1); every week for first 12 weeks, Days 1 and 22 of each cycle (Cycle 3 up to 19), within 30 days of PD (up to 27 months), at EoT (up to 27 months) and at 6, 12, 24, and 36 weeks after EoT (overall up to 27 months); 1 cycle=42 days

End point values	Sunitinib	Atezolizumab + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	368	381		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=368,381)	2.11 (± 2.23)	2.08 (± 2.38)		
Change at Cycle 1 Day 8 (n=352,356)	0.30 (± 1.88)	0.37 (± 1.76)		
Change at Cycle 1 Day 15 (n=339,352)	1.26 (± 2.49)	1.06 (± 2.42)		
Change at Cycle 1 Day 22 (n=258,298)	1.34 (± 2.44)	0.57 (± 2.04)		

Change at Cycle 1 Day 29 (n=329,348)	1.48 (± 2.63)	0.66 (± 2.28)		
Change at Cycle 1 Day 36 (n=311,344)	0.95 (± 2.29)	0.74 (± 2.20)		
Change at Cycle 2 Day 1 (n=271,293)	0.38 (± 2.03)	0.43 (± 2.09)		
Change at Cycle 2 Day 8 (n=307,336)	0.63 (± 2.17)	0.68 (± 2.33)		
Change at Cycle 2 Day 15 (n=310,319)	1.10 (± 2.35)	0.55 (± 2.29)		
Change at Cycle 2 Day 22 (n=245,277)	1.24 (± 2.65)	0.26 (± 2.14)		
Change at Cycle 2 Day 29 (n=302,303)	1.45 (± 2.61)	0.51 (± 2.14)		
Change at Cycle 2 Day 36 (n=291,311)	1.11 (± 2.46)	0.43 (± 2.17)		
Change at Cycle 3 Day 1 (n=238,278)	0.76 (± 2.27)	0.21 (± 2.12)		
Change at Cycle 3 Day 22 (n=229,279)	1.43 (± 2.41)	0.36 (± 2.20)		
Change at Cycle 4 Day 1 (n=231,266)	0.76 (± 2.27)	0.38 (± 2.16)		
Change at Cycle 4 Day 22 (n=219,252)	1.47 (± 2.60)	0.44 (± 2.33)		
Change at Cycle 5 Day 1 (n=212,239)	1.01 (± 2.46)	0.52 (± 2.31)		
Change at Cycle 5 Day 22 (n=197,238)	1.38 (± 2.22)	0.61 (± 2.27)		
Change at Cycle 6 Day 1 (n=199,224)	0.88 (± 2.24)	0.59 (± 2.15)		
Change at Cycle 6 Day 22 (n=184,207)	1.25 (± 2.42)	0.52 (± 2.22)		
Change at Cycle 7 Day 1 (n=174,200)	0.82 (± 2.35)	0.61 (± 2.17)		
Change at Cycle 7 Day 22 (n=164,191)	1.05 (± 2.31)	0.47 (± 2.16)		
Change at Cycle 8 Day 1 (n=162,192)	0.87 (± 2.21)	0.63 (± 2.36)		
Change at Cycle 8 Day 22 (n=151,186)	1.22 (± 2.21)	0.52 (± 2.05)		
Change at Cycle 9 Day 1 (n=147,185)	0.93 (± 2.25)	0.57 (± 2.27)		
Change at Cycle 9 Day 22 (n=136,172)	1.35 (± 2.37)	0.37 (± 2.15)		
Change at Cycle 10 Day 1 (n=132,169)	1.09 (± 2.53)	0.56 (± 1.96)		
Change at Cycle 10 Day 22 (n=78,151)	1.62 (± 2.75)	0.52 (± 1.95)		
Change at Cycle 11 Day 1 (n=101,134)	0.95 (± 2.29)	0.60 (± 1.92)		
Change at Cycle 11 Day 22 (n=59,122)	0.88 (± 2.57)	0.57 (± 1.78)		
Change at Cycle 12 Day 1 (n=73,111)	0.89 (± 2.45)	0.35 (± 1.75)		
Change at Cycle 12 Day 22 (n=47,93)	0.97 (± 2.46)	0.58 (± 1.96)		
Change at Cycle 13 Day 1 (n=52,81)	0.84 (± 2.29)	0.36 (± 1.88)		
Change at Cycle 13 Day 22 (n=36,72)	0.76 (± 2.70)	0.56 (± 2.06)		
Change at Cycle 14 Day 1 (n=39,57)	0.80 (± 2.33)	0.73 (± 1.80)		
Change at Cycle 14 Day 22 (n=27,54)	0.69 (± 2.73)	0.94 (± 1.96)		
Change at Cycle 15 Day 1 (n=31,43)	0.95 (± 2.42)	0.61 (± 1.41)		
Change at Cycle 15 Day 22 (n=17,36)	1.05 (± 3.22)	0.91 (± 1.28)		
Change at Cycle 16 Day 1 (n=20,27)	0.13 (± 1.49)	1.02 (± 1.69)		
Change at Cycle 16 Day 22 (n=13,22)	1.05 (± 1.83)	1.55 (± 1.96)		
Change at Cycle 17 Day 1 (n=13,19)	0.53 (± 1.41)	1.25 (± 1.97)		
Change at Cycle 17 Day 22 (n=9,11)	1.43 (± 2.16)	0.41 (± 1.48)		
Change at Cycle 18 Day 1 (n=7,9)	0.79 (± 1.34)	0.35 (± 1.46)		
Change at Cycle 18 Day 22 (n=3,6)	1.28 (± 2.21)	0.17 (± 1.15)		
Change at Cycle 19 Day 1 (n=1,5)	0.00 (± 99999)	-0.80 (± 0.84)		
Change at Cycle 19 Day 22 (n=0,2)	9999 (± 9999)	-0.25 (± 0.82)		
Change at 6 weeks after EoT (n=70,42)	2.31 (± 2.52)	1.83 (± 2.52)		
Change at 12 weeks after EoT (n=59,36)	1.71 (± 2.66)	1.97 (± 2.63)		
Change at 24 weeks after EoT (n=31,25)	2.38 (± 3.11)	2.15 (± 3.30)		
Change at 36 weeks after EoT (n=14,18)	2.40 (± 3.32)	1.15 (± 2.72)		
Change at EoT (n=168,127)	1.57 (± 2.80)	1.62 (± 2.98)		
Change Within 30 Days of PD (n=194,184)	1.74 (± 2.64)	0.74 (± 2.35)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Symptom Severity as Determined by BFI Worst Fatigue Item

End point title	Change from Baseline in Symptom Severity as Determined by BFI Worst Fatigue Item

End point description:

The BFI is a valid and reliable self-report questionnaire used to assess the severity and impact of cancer-related fatigue. BFI worst fatigue item assessed the severity of fatigue at its worst in the last 24 hours. The item was rated on a scale of 0 (not present) to 10 (as bad as you can imagine). Change from baseline in the score at each time point is reported, where a negative value indicates improvement. Analysis was performed on the PRO-Evaluable Population. Here, 'Number of Subject Analysed' = number of participants evaluable for this outcome measure; 'n'= number of participants evaluable at specified time point for different arms, respectively; '9999' = data not available as no participant was evaluable at specified time point; and '99999' = SD could not be estimated as only 1 participant was evaluable.

End point type	Secondary

End point timeframe:

Baseline (Day 1 Cycle 1); every week for first 12 weeks, Days 1 and 22 of each cycle (Cycle 3 up to 19), within 30 days of PD (up to 27 months), at EoT (up to 27 months) and at 6, 12, 24, and 36 weeks after EoT (overall up to 27 months); 1 cycle=42 days

End point values	Sunitinib	Atezolizumab + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	368	381		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=368,381)	3.08 (± 2.66)	2.98 (± 2.69)		
Change at Cycle 1 Day 8 (n=352,356)	0.34 (± 2.35)	0.50 (± 2.29)		
Change at Cycle 1 Day 15 (n=339,352)	1.32 (± 2.82)	1.26 (± 2.92)		
Change at Cycle 1 Day 22 (n=258,298)	1.52 (± 2.86)	0.49 (± 2.30)		
Change at Cycle 1 Day 29 (n=329,348)	1.55 (± 2.99)	0.88 (± 2.62)		
Change at Cycle 1 Day 36 (n=311,344)	0.77 (± 2.82)	0.86 (± 2.50)		
Change at Cycle 2 Day 1 (n=271,293)	0.40 (± 2.50)	0.45 (± 2.52)		
Change at Cycle 2 Day 8 (n=307,336)	0.56 (± 2.68)	0.87 (± 2.82)		
Change at Cycle 2 Day 15 (n=310,319)	1.09 (± 2.82)	0.71 (± 2.78)		
Change at Cycle 2 Day 22 (n=245,277)	1.42 (± 3.01)	0.31 (± 2.53)		
Change at Cycle 2 Day 29 (n=302,303)	1.43 (± 3.08)	0.62 (± 2.66)		
Change at Cycle 2 Day 36 (n=291,311)	1.09 (± 3.01)	0.48 (± 2.76)		
Change at Cycle 3 Day 1 (n=238,278)	0.42 (± 2.68)	0.40 (± 2.57)		
Change at Cycle 3 Day 22 (n=229,279)	1.57 (± 2.98)	0.57 (± 2.64)		
Change at Cycle 4 Day 1 (n=231,266)	0.64 (± 2.76)	0.54 (± 2.49)		
Change at Cycle 4 Day 22 (n=219,252)	1.46 (± 3.14)	0.58 (± 2.74)		
Change at Cycle 5 Day 1 (n=212,239)	0.81 (± 2.75)	0.62 (± 2.79)		

Change at Cycle 5 Day 22 (n=197,238)	1.60 (± 2.87)	0.69 (± 2.83)		
Change at Cycle 6 Day 1 (n=199,224)	0.90 (± 2.78)	0.86 (± 2.73)		
Change at Cycle 6 Day 22 (n=184,207)	1.35 (± 2.79)	0.53 (± 2.66)		
Change at Cycle 7 Day 1 (n=174,200)	0.79 (± 2.78)	0.79 (± 2.70)		
Change at Cycle 7 Day 22 (n=164,191)	1.22 (± 2.85)	0.65 (± 2.56)		
Change at Cycle 8 Day 1 (n=162,192)	0.79 (± 2.69)	0.75 (± 2.84)		
Change at Cycle 8 Day 22 (n=151,186)	1.40 (± 2.64)	0.78 (± 2.67)		
Change at Cycle 9 Day 1 (n=147,185)	0.97 (± 2.54)	0.61 (± 2.62)		
Change at Cycle 9 Day 22 (n=136,172)	1.54 (± 2.92)	0.57 (± 2.55)		
Change at Cycle 10 Day 1 (n=132,169)	0.95 (± 2.73)	0.69 (± 2.46)		
Change at Cycle 10 Day 22 (n=78,151)	1.74 (± 3.09)	0.63 (± 2.48)		
Change at Cycle 11 Day 1 (n=101,134)	0.73 (± 2.80)	0.74 (± 2.69)		
Change at Cycle 11 Day 22 (n=59,122)	1.15 (± 3.18)	0.74 (± 2.52)		
Change at Cycle 12 Day 1 (n=73,111)	0.78 (± 2.79)	0.61 (± 2.29)		
Change at Cycle 12 Day 22 (n=47,93)	1.32 (± 2.89)	0.74 (± 2.69)		
Change at Cycle 13 Day 1 (n=52,81)	0.35 (± 2.54)	0.49 (± 2.46)		
Change at Cycle 13 Day 22 (n=36,72)	0.72 (± 3.48)	0.65 (± 2.70)		
Change at Cycle 14 Day 1 (n=39,57)	0.56 (± 2.84)	0.81 (± 2.60)		
Change at Cycle 14 Day 22 (n=27,54)	0.37 (± 3.01)	1.04 (± 2.40)		
Change at Cycle 15 Day 1 (n=31,43)	0.52 (± 3.15)	0.93 (± 2.25)		
Change at Cycle 15 Day 22 (n=17,36)	0.59 (± 4.08)	0.97 (± 1.84)		
Change at Cycle 16 Day 1 (n=20,27)	-0.05 (± 2.61)	1.33 (± 1.92)		
Change at Cycle 16 Day 22 (n=13,22)	0.77 (± 3.70)	1.68 (± 2.10)		
Change at Cycle 17 Day 1 (n=13,19)	-0.62 (± 3.75)	1.68 (± 1.97)		
Change at Cycle 17 Day 22 (n=9,11)	1.44 (± 3.91)	1.18 (± 1.99)		
Change at Cycle 18 Day 1 (n=7,9)	0.00 (± 2.00)	1.33 (± 1.58)		
Change at Cycle 18 Day 22 (n=3,6)	1.00 (± 1.73)	1.00 (± 2.10)		
Change at Cycle 19 Day 1 (n=1,5)	-4.00 (± 99999)	0.60 (± 1.34)		
Change at Cycle 19 Day 22 (n=0,2)	9999 (± 9999)	0.00 (± 0.00)		
Change at 6 weeks after EoT (n=70,42)	2.43 (± 3.25)	2.40 (± 2.89)		
Change at 12 weeks after EoT (n=59,36)	1.56 (± 3.41)	2.06 (± 3.14)		
Change at 24 weeks after EoT (n=31,25)	1.58 (± 3.82)	1.92 (± 3.46)		
Change at 36 weeks after EoT (n=14,18)	1.86 (± 4.37)	0.78 (± 2.86)		
Change at EoT (n=168,127)	1.40 (± 3.13)	1.72 (± 2.84)		
Change Within 30 Days of PD (n=194,184)	1.81 (± 3.16)	0.89 (± 2.58)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Treatment Side Effects Burden as Determined by Functional Assessment of Cancer Therapy Kidney Symptom Index (FKSI-19) General Population 5 (GP5) Item Score

End point title	Change from Baseline in Treatment Side Effects Burden as Determined by Functional Assessment of Cancer Therapy Kidney Symptom Index (FKSI-19) General Population 5 (GP5) Item Score

End point description:

The FKSI-19 is a 19-item tool designed to assess the most important symptoms and concerns related to treatment effectiveness in advanced kidney cancer. The FKSI-19 GP5 item (bothered by the side effect of treatment) assessed side effects burden in the past 7 days on a 5-point scale (0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit, 4=very much). Repeated measures model-estimated LS mean score for changes from baseline is reported at each timepoint, where a negative value indicates improvement. Analysis was performed on the PRO-Evaluable Population. Here, 'n'= number of participants evaluable at specified time point for different arms, respectively. '99999' = data not available as no participant was evaluable at specified time point.

End point type	Secondary

End point timeframe:

Day 1 and 22 of every cycle (Baseline = Day 1 Cycle 1) up to Cycle 19; Cycle length = 42 days

End point values	Sunitinib	Atezolizumab + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	359	373		
Units: units on a scale				
least squares mean (standard error)				
Change at Cycle1 Day 22 (n=260,301)	-1.08 (± 0.06)	-0.36 (± 0.06)		
Change at Cycle 2 Day 1 (n=276,305)	-0.87 (± 0.06)	-0.45 (± 0.06)		
Change at Cycle 2 Day 22 (n=248,283)	-1.13 (± 0.06)	-0.43 (± 0.06)		
Change at Cycle 3 Day 1 (n=253,297)	-1.07 (± 0.06)	-0.49 (± 0.06)		
Change at Cycle 3 Day 22 (n=226,279)	-1.22 (± 0.06)	-0.45 (± 0.06)		
Change at Cycle 4 Day 1 (n=230,266)	-1.07 (± 0.06)	-0.45 (± 0.06)		
Change at Cycle 4 Day 22 (n=215,252)	-1.31 (± 0.07)	-0.49 (± 0.06)		
Change at Cycle 5 Day 1 (n=210,238)	-1.17 (± 0.07)	-0.52 (± 0.06)		
Change at Cycle 5 Day 22 (n=196,238)	-1.38 (± 0.07)	-0.55 (± 0.06)		
Change at Cycle 6 Day 1 (n=198,223)	-1.14 (± 0.07)	-0.51 (± 0.06)		
Change at Cycle 6 Day 22 (n=183,207)	-1.27 (± 0.07)	-0.56 (± 0.07)		
Change at Cycle 7 Day 1 (n=173,200)	-1.09 (± 0.07)	-0.61 (± 0.07)		
Change at Cycle 7 Day 22 (n=163,191)	-1.25 (± 0.07)	-0.58 (± 0.07)		
Change at Cycle 8 Day 1 (n=161,191)	-1.08 (± 0.08)	-0.61 (± 0.07)		
Change at Cycle 8 Day 22 (n=150,186)	-1.22 (± 0.08)	-0.62 (± 0.07)		
Change at Cycle 9 Day 1 (n=146,185)	-1.08 (± 0.08)	-0.60 (± 0.07)		
Change at Cycle 9 Day 22 (n=135,172)	-1.23 (± 0.08)	-0.52 (± 0.07)		
Change at Cycle 10 Day 1 (n=131,169)	-1.06 (± 0.08)	-0.53 (± 0.07)		
Change at Cycle 10 Day 22 (n=77,150)	-1.30 (± 0.09)	-0.57 (± 0.08)		
Change at Cycle 11 Day 1 (n=100,134)	-1.16 (± 0.09)	-0.52 (± 0.08)		
Change at Cycle 11 Day 22 (n=59,122)	-1.28 (± 0.11)	-0.54 (± 0.08)		
Change at Cycle 12 Day 1 (n=73,110)	-1.05 (± 0.10)	-0.62 (± 0.09)		
Change at Cycle 12 Day 22 (n=47,93)	-1.17 (± 0.12)	-0.56 (± 0.09)		
Change at Cycle 13 Day 1 (n=52,81)	-1.15 (± 0.12)	-0.62 (± 0.10)		
Change at Cycle 13 Day 22 (n=36,72)	-1.20 (± 0.14)	-0.64 (± 0.11)		
Change at Cycle 14 Day 1 (n=39,57)	-0.94 (± 0.14)	-0.61 (± 0.12)		
Change at Cycle 14 Day 22 (n=27,54)	-1.32 (± 0.16)	-0.65 (± 0.12)		
Change at Cycle 15 Day 1 (n=31,43)	-0.91 (± 0.15)	-0.62 (± 0.13)		
Change at Cycle 15 Day 22 (n=17,36)	-1.16 (± 0.19)	-0.72 (± 0.14)		
Change at Cycle 16 Day 1 (n=20,27)	-1.06 (± 0.19)	-0.58 (± 0.16)		
Change at Cycle 16 Day 22 (n=13,22)	-1.34 (± 0.22)	-0.41 (± 0.18)		
Change at Cycle 17 Day 1 (n=13,19)	-1.10 (± 0.23)	-0.56 (± 0.20)		

Change at Cycle 17 Day 22 (n=9,11)	-1.02 (± 0.27)	-0.44 (± 0.24)		
Change at Cycle 18 Day 1 (n=6,9)	-1.01 (± 0.33)	-0.38 (± 0.27)		
Change at Cycle 18 Day 22 (n=3,6)	-0.81 (± 0.46)	-0.48 (± 0.33)		
Change at Cycle 19 Day 1 (n=1,5)	-1.27 (± 0.84)	-0.75 (± 0.38)		
Change at Cycle 19 Day 22 (n=0,2)	99999 (± 99999)	-0.93 (± 0.55)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Cycle 1 Day 22 (Actual number of participants included in the analysis = 561): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[74]
P-value	< 0.0001
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	0.87

Notes:

[74] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Cycle 2 Day 1 (Actual number of participants included in the analysis = 581): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[75]
P-value	< 0.0001
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	0.42

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.28
upper limit	0.57

Notes:

[75] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Cycle 2 Day 22 (Actual number of participants included in the analysis = 531): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[76]
P-value	< 0.0001
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	0.84

Notes:

[76] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

Cycle 3 Day 1 (Actual number of participants included in the analysis = 550): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[77]
P-value	< 0.0001
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	0.73

Notes:

[77] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 5

Statistical analysis description:

Cycle 3 Day 22 (Actual number of participants included in the analysis = 505): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[78]
P-value	< 0.0001
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	0.92

Notes:

[78] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 6

Statistical analysis description:

Cycle 4 Day 1 (Actual number of participants included in the analysis = 496): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[79]
P-value	< 0.0001
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	0.78

Notes:

[79] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 7

Statistical analysis description:

Cycle 4 Day 22 (Actual number of participants included in the analysis = 467): Repeated measures

model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[80]
P-value	< 0.0001
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	0.97

Notes:

[80] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 8

Statistical analysis description:

Cycle 5 Day 1 (Actual number of participants included in the analysis = 448): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[81]
P-value	< 0.0001
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	0.81

Notes:

[81] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 9

Statistical analysis description:

Cycle 5 Day 22 (Actual number of participants included in the analysis = 434): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab

Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[82]
P-value	< 0.0001
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	0.99

Notes:

[82] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 10

Statistical analysis description:

Cycle 6 Day 1 (Actual number of participants included in the analysis = 421): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[83]
P-value	< 0.0001
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	0.8

Notes:

[83] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 11

Statistical analysis description:

Cycle 6 Day 22 (Actual number of participants included in the analysis = 390): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[84]
P-value	< 0.0001
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	0.72

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	0.89

Notes:

[84] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 12

Statistical analysis description:

Cycle 7 Day 1 (Actual number of participants included in the analysis = 373): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[85]
P-value	< 0.0001
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	0.65

Notes:

[85] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 13

Statistical analysis description:

Cycle 7 Day 22 (Actual number of participants included in the analysis = 354): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[86]
P-value	< 0.0001
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	0.86

Notes:

[86] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 14

Statistical analysis description:

Cycle 8 Day 1 (Actual number of participants included in the analysis = 352): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[87]
P-value	< 0.0001
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.29
upper limit	0.66

Notes:

[87] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 16

Statistical analysis description:

Cycle 9 Day 1 (Actual number of participants included in the analysis = 331): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[88]
P-value	< 0.0001
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.29
upper limit	0.68

Notes:

[88] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 15

Statistical analysis description:

Cycle 8 Day 22 (Actual number of participants included in the analysis = 336): Repeated measures

model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[89]
P-value	< 0.0001
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	0.79

Notes:

[89] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 17

Statistical analysis description:

Cycle 9 Day 22 (Actual number of participants included in the analysis = 307): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[90]
P-value	< 0.0001
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	0.91

Notes:

[90] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 19

Statistical analysis description:

Cycle 10 Day 22 (Actual number of participants included in the analysis = 227): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab

Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[91]
P-value	< 0.0001
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	0.96

Notes:

[91] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 18

Statistical analysis description:

Cycle 10 Day 1 (Actual number of participants included in the analysis = 300): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[92]
P-value	< 0.0001
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.33
upper limit	0.73

Notes:

[92] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 20

Statistical analysis description:

Cycle 11 Day 1 (Actual number of participants included in the analysis = 234): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[93]
P-value	< 0.0001
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	0.64

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	0.86

Notes:

[93] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 21

Statistical analysis description:

Cycle 11 Day 22 (Actual number of participants included in the analysis = 181): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[94]
P-value	< 0.0001
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	0.99

Notes:

[94] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 22

Statistical analysis description:

Cycle 12 Day 1 (Actual number of participants included in the analysis = 183): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[95]
P-value	= 0.001
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.17
upper limit	0.68

Notes:

[95] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 23

Statistical analysis description:

Cycle 12 Day 22 (Actual number of participants included in the analysis = 140): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[96]
P-value	< 0.0001
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.32
upper limit	0.89

Notes:

[96] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 24

Statistical analysis description:

Cycle 13 Day 1 (Actual number of participants included in the analysis = 133): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[97]
P-value	= 0.0005
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.23
upper limit	0.82

Notes:

[97] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 25

Statistical analysis description:

Cycle 13 Day 22 (Actual number of participants included in the analysis = 108): Repeated measures

model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[98]
P-value	= 0.0008
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.23
upper limit	0.88

Notes:

[98] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 27

Statistical analysis description:

Cycle 14 Day 22 (Actual number of participants included in the analysis = 81): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[99]
P-value	= 0.0005
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.29
upper limit	1.05

Notes:

[99] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 26

Statistical analysis description:

Cycle 14 Day 1 (Actual number of participants included in the analysis = 96): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab

Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[100]
P-value	= 0.0591
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	0.67

Notes:

[100] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 28

Statistical analysis description:

Cycle 15 Day 1 (Actual number of participants included in the analysis = 74): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[101]
P-value	= 0.1378
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.09
upper limit	0.68

Notes:

[101] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 29

Statistical analysis description:

Cycle 15 Day 22 (Actual number of participants included in the analysis = 53): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[102]
P-value	= 0.065
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	0.43

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.89

Notes:

[102] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 30

Statistical analysis description:

Cycle 16 Day 1 (Actual number of participants included in the analysis = 47): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[103]
P-value	= 0.0531
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	0.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	0.96

Notes:

[103] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 31

Statistical analysis description:

Cycle 16 Day 22 (Actual number of participants included in the analysis = 35): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[104]
P-value	= 0.0011
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.37
upper limit	1.49

Notes:

[104] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 33

Statistical analysis description:

Cycle 17 Day 22 (Actual number of participants included in the analysis = 20): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[105]
P-value	= 0.1078
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.13
upper limit	1.29

Notes:

[105] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 32

Statistical analysis description:

Cycle 17 Day 1 (Actual number of participants included in the analysis = 32): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[106]
P-value	= 0.0708
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	0.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	1.14

Notes:

[106] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 34

Statistical analysis description:

Cycle 18 Day 1 (Actual number of participants included in the analysis = 15): Repeated measures

model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[107]
P-value	= 0.1487
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.22
upper limit	1.47

Notes:

[107] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 35

Statistical analysis description:

Cycle 18 Day 22 (Actual number of participants included in the analysis = 9): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab
Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[108]
P-value	= 0.5537
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.77
upper limit	1.43

Notes:

[108] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Statistical analysis title	Statistical Analysis 36

Statistical analysis description:

Cycle 19 Day 1 (Actual number of participants included in the analysis = 6): Repeated measures model, assuming 1st order autoregressive covariance structure, with a term for visit as a categorical variable, a term for treatment group, a term for treatment-by-visit interaction, baseline score and stratification factors (presence of liver metastasis, PD-L1 status, and Motzer score) included as covariates in the model.

Comparison groups	Sunitinib v Atezolizumab + Bevacizumab

Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority[109]
P-value	= 0.5743
Method	Repeated measures model
Parameter estimate	LS Mean Difference
Point estimate	0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.29
upper limit	2.33

Notes:

[109] - Difference in LS mean score change between arms (Atezolizumab + Bevacizumab minus Sunitinib) was reported.

Secondary: Number of Participants with Anti-Therapeutic Antibodies (ATAs) Against Atezolizumab

End point title	Number of Participants with Anti-Therapeutic Antibodies (ATAs) Against Atezolizumab[110]

End point description:

The number of participants with "Treatment-induced ATAs" and "Treatment-enhanced ATA" against atezolizumab at any time during or after treatment was reported. Treatment-induced ATA = a participant with negative or missing Baseline ATA result(s) and at least one positive post-Baseline ATA result. Treatment-enhanced ATA = a participant with positive ATA result at Baseline who has one or more post Baseline titer results that are at least 0.60 titer unit greater than the Baseline titer result. Analysis was performed on the ATA-Evaluable Population, which included all participants in the Atezolizumab + Bevacizumab arm with a non-missing baseline ATA sample and >/=1 post-baseline ATA sample. Here, 'Number of Subject Analysed' = number of participants with a non-missing baseline ATA sample; 'n'= number of participants with a non-missing ATA sample at indicated timepoint.

End point type	Secondary

End point timeframe:

Baseline (Predose [Hour 0] at Day 1 Cycle 1); Post-Baseline (Predose at Cycles 2, 4, and 8, and every eight cycles thereafter up to EoT [up to approximately 27 months] and 120 days after EoT [up to approximately 27 months]) (Cycle length=42 days)

Notes:

[110] - 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: Reported analysis was planned to be carried out in the indicated arm only.

End point values	Atezolizumab + Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	446			
Units: participants				
number (not applicable)				
Baseline: ATA Positive Participants (n=446)	16			
Post-Baseline: Treatment-Induced ATA (n=433)	95			
Post-Baseline: Treatment-Enhanced ATA (n=433)	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with ATAs Against Bevacizumab

End point title	Number of Participants with ATAs Against Bevacizumab[111]

End point description:

The number of participants with "Treatment-induced ATAs" and "Treatment-enhanced ATA" against bevacizumab at any time during or after treatment was reported. Treatment-induced ATA = a participant with negative or missing Baseline ATA result(s) and at least one positive post-Baseline ATA result. Treatment-enhanced ATA = a participant with positive ATA result at Baseline who has one or more post Baseline titer results that are at least 0.60 titer unit greater than the Baseline titer result. Analysis was performed on the ATA-Evaluable Population. Here, 'Number of Subject Analysed' = number of participants with a non-missing baseline ATA sample; 'n'= number of participants with a non-missing ATA sample at indicated timepoint.

End point type	Secondary

End point timeframe:

Baseline (Predose [Hour 0] at Day 1 Cycle 1); Post-Baseline (Predose at Cycle 3, at EoT [up to approximately 27 months] and at 120 days after EoT [up to approximately 27 months]) (Cycle length=42 days)

Notes:

[111] - 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: Reported analysis was planned to be carried out in the indicated arm only.

End point values	Atezolizumab + Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	444			
Units: participants				
number (not applicable)				
Baseline: ATA Positive Participants (n=444)	24			
Post-Baseline: Treatment-Induced ATA (n=433)	4			
Post-Baseline: Treatment-Enhanced ATA (n=433)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Observed Serum Concentration (Cmin) for Atezolizumab

End point title	Minimum Observed Serum Concentration (Cmin) for Atezolizumab[112]

End point description:

Cmin for atezolizumab was estimated from plasma concentration versus time data. Analysis was performed on the Atezolizumab PK Population. Here, 'Number of Subject Analysed' = number of participants evaluable for this outcome measure; 'n' = number of participants evaluable at specified time point.

End point type	Secondary

End point timeframe:

Predose (Hour 0) on Day 22 of Cycle 1; predose (Hour 0) on Day 1 of Cycles 2; Cycle length = 42 days

Notes:

[112] - 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: Reported analysis was planned to be carried out in the indicated arm only.

End point values	Atezolizumab + Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	426			
Units: mcg/mL				
arithmetic mean (standard deviation)				
Cycle 1 Day 22 (n=426) Cycle 2 Day 1 (n=407)	85.6 (± 35.3) 127 (± 49.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Serum Concentration (Cmax) for Atezolizumab

End point title	Maximum Observed Serum Concentration (Cmax) for Atezolizumab[113]

End point description:

Cmax for atezolizumab was estimated from plasma concentration versus time data. Analysis was performed on the Atezolizumab Pharmacokinetic (PK) Population, which included all participants who received atezolizumab treatment and had evaluable PK samples. Here, 'Number of Subject Analysed' = number of participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

30 minutes after the end of bevacizumab infusion (atezolizumab infusion duration: 30-60 min; bevacizumab infusion duration: 30-90 minutes) on Day 1 of Cycle 1 (Cycle length = 42 days)

Notes:

[113] - 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: Reported analysis was planned to be carried out in the indicated arm only.

End point values	Atezolizumab + Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	435			
Units: micrograms per milliliter (mcg/mL)				
arithmetic mean (standard deviation)	376 (± 90.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax for Bevacizumab

End point title	Cmax for Bevacizumab[114]

End point description:

Cmax for bevacizumab was estimated from plasma concentration versus time data. Analysis was performed on the Bevacizumab PK Population, which included all participants who received bevacizumab treatment and had evaluable PK samples. Here, 'Number of Subject Analysed' = number of participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

30 minutes after the end of bevacizumab infusion (atezolizumab infusion duration: 30-60 min; bevacizumab infusion duration: 30-90 minutes) on Day 1 of Cycle 1 (Cycle length = 42 days)

Notes:

[114] - 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: Reported analysis was planned to be carried out in the indicated arm only.

End point values	Atezolizumab + Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	427			
Units: mcg/mL				
arithmetic mean (standard deviation)	339 (± 104)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cmin for Bevacizumab

End point title	Cmin for Bevacizumab[115]

End point description:

Cmin for bevacizumab was estimated from plasma concentration versus time data. Analysis was performed on the Bevacizumab PK Population. Here, 'Number of Subject Analysed' = number of participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Pre-dose (Hour 0) on Day 1 of Cycle 3 (Cycle length = 42 days)

Notes:

[115] - 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: Reported analysis was planned to be carried out in the indicated arm only.

End point values	Atezolizumab + Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	363			
Units: mcg/mL				
arithmetic mean (standard deviation)	135 (± 56.1)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to data cut-off date 29 September 2017 (overall approximately 27 months)

Adverse event reporting additional description:

Analysis was performed on the safety-evaluable (SE) population, which included all randomized participants who received any amount of any component of the study treatments.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Sunitinib

Reporting group description:

Participants received sunitinib at a dose of 50 mg administered orally via capsules once daily on Days 1 to 28 of each 42-day cycle until loss of clinical benefit in the opinion of the investigator, unacceptable toxicity or symptomatic deterioration attributed to PD as determined by the investigator, withdrawal of consent, or death, whichever occurred first.

Reporting group title	Atezolizumab + Bevacizumab

Reporting group description:

Participants received atezolizumab at a dose of 1200 mg and bevacizumab at a dose of 15 mg/kg administered via IV infusions on Day 1 and Day 22 of each 42-day cycle until loss of clinical benefit in the opinion of the investigator, unacceptable toxicity or symptomatic deterioration attributed to PD as determined by the investigator, withdrawal of consent, or death, whichever occurred first.

Serious adverse events	Sunitinib	Atezolizumab + Bevacizumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	149 / 446 (33.41%)	174 / 451 (38.58%)	
number of deaths (all causes)	135	122	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon neoplasm			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			

subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangiocarcinoma			
subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer stage III			
subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial tumour haemorrhage			
subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 446 (0.00%)	2 / 451 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 446 (0.22%)	2 / 451 (0.44%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 446 (0.22%)	2 / 451 (0.44%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic disorder			

subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic dissection			
subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery aneurysm			
subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Fracture treatment			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernia repair			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth extraction			
subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

Pyrexia			
subjects affected / exposed	7 / 446 (1.57%)	12 / 451 (2.66%)	
occurrences causally related to treatment / all	1 / 8	10 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	3 / 446 (0.67%)	3 / 451 (0.67%)	
occurrences causally related to treatment / all	3 / 4	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness			
subjects affected / exposed	1 / 446 (0.22%)	3 / 451 (0.67%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 446 (0.00%)	3 / 451 (0.67%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	0 / 446 (0.00%)	2 / 451 (0.44%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	4 / 446 (0.90%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	2 / 446 (0.45%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			

subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ill-defined disorder			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Infusion site extravasation			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 446 (0.22%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Non-cardiac chest pain			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Performance status decreased			

subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Systemic immune activation			
subjects affected / exposed	0 / 446 (0.00%)	3 / 451 (0.67%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytokine release syndrome			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug hypersensitivity			
subjects affected / exposed	1 / 446 (0.22%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	0 / 446 (0.00%)	7 / 451 (1.55%)	
occurrences causally related to treatment / all	0 / 0	7 / 8	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dyspnoea			
subjects affected / exposed	5 / 446 (1.12%)	4 / 451 (0.89%)	
occurrences causally related to treatment / all	0 / 6	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	5 / 446 (1.12%)	4 / 451 (0.89%)	
occurrences causally related to treatment / all	1 / 5	3 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 446 (0.22%)	3 / 451 (0.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	0 / 446 (0.00%)	2 / 451 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypoxia			
subjects affected / exposed	1 / 446 (0.22%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
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 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary infarction			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary pain			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			
subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (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	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal oedema			
subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 446 (0.00%)	2 / 451 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			

subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 446 (0.22%)	2 / 451 (0.44%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood sodium decreased			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipase increased			
subjects affected / exposed	1 / 446 (0.22%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test increased			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			

subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin increased			
subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Conjunctival laceration			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
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 / 446 (0.22%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	2 / 446 (0.45%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal anastomotic leak			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
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 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			

subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound complication			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Seroma			
subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth injury			
subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 446 (0.00%)	3 / 451 (0.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial infarction			

subjects affected / exposed	0 / 446 (0.00%)	3 / 451 (0.67%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute coronary syndrome			
subjects affected / exposed	1 / 446 (0.22%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 446 (0.22%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 446 (0.22%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 1	
Myocarditis			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Haemorrhage intracranial			
subjects affected / exposed	0 / 446 (0.00%)	2 / 451 (0.44%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Ischaemic stroke			

subjects affected / exposed	0 / 446 (0.00%)	2 / 451 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	2 / 446 (0.45%)	2 / 451 (0.44%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 446 (0.22%)	2 / 451 (0.44%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Altered state of consciousness			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphasia			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Coma			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			

subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gliosis			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	1 / 446 (0.22%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial pressure increased			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbosacral plexopathy			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			

subjects affected / exposed	1 / 446 (0.22%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	2 / 446 (0.45%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	2 / 446 (0.45%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lacunar infarction			
subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraplegia			
subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thalamus haemorrhage			
subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	3 / 446 (0.67%)	3 / 451 (0.67%)	
occurrences causally related to treatment / all	1 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	2 / 446 (0.45%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	4 / 446 (0.90%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Factor VIII inhibition			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 446 (0.45%)	7 / 451 (1.55%)	
occurrences causally related to treatment / all	2 / 2	4 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	2 / 446 (0.45%)	4 / 451 (0.89%)	
occurrences causally related to treatment / all	1 / 2	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 446 (0.22%)	4 / 451 (0.89%)	
occurrences causally related to treatment / all	1 / 1	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	5 / 446 (1.12%)	3 / 451 (0.67%)	
occurrences causally related to treatment / all	3 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 446 (0.22%)	2 / 451 (0.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Abdominal pain upper			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune colitis			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 446 (0.22%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal obstruction			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	1 / 446 (0.22%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			

subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
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 / 446 (0.22%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	1 / 446 (0.22%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Large intestine perforation			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 446 (0.22%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	3 / 446 (0.67%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	2 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal perforation			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	2 / 446 (0.45%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal haemorrhage			

subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal perforation			
subjects affected / exposed	1 / 446 (0.22%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 446 (0.22%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 446 (0.22%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	2 / 446 (0.45%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal fistula			
subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	0 / 446 (0.00%)	4 / 451 (0.89%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary colic			

subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 446 (0.22%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	1 / 446 (0.22%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	1 / 446 (0.22%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic steatosis			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			

subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash macular			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic epidermal necrolysis			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	10 / 446 (2.24%)	9 / 451 (2.00%)	
occurrences causally related to treatment / all	5 / 10	2 / 9	
deaths causally related to treatment / all	0 / 0	0 / 2	
Proteinuria			
subjects affected / exposed	0 / 446 (0.00%)	3 / 451 (0.67%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 446 (0.00%)	2 / 451 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	3 / 446 (0.67%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephritis			

subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrotic syndrome			
subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric obstruction			
subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			

subjects affected / exposed	0 / 446 (0.00%)	2 / 451 (0.44%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Hypothyroidism			
subjects affected / exposed	6 / 446 (1.35%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	6 / 6	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 446 (0.22%)	4 / 451 (0.89%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	1 / 446 (0.22%)	3 / 451 (0.67%)	
occurrences causally related to treatment / all	1 / 1	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	1 / 446 (0.22%)	2 / 451 (0.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 446 (0.00%)	2 / 451 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	3 / 446 (0.67%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint swelling			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mobility decreased			

subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myositis			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fistula			
subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin pain			
subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	2 / 446 (0.45%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle haemorrhage			

subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (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	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	4 / 446 (0.90%)	7 / 451 (1.55%)	
occurrences causally related to treatment / all	0 / 4	1 / 8	
deaths causally related to treatment / all	0 / 1	0 / 1	
Sepsis			
subjects affected / exposed	2 / 446 (0.45%)	3 / 451 (0.67%)	
occurrences causally related to treatment / all	0 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Diverticulitis			
subjects affected / exposed	1 / 446 (0.22%)	2 / 451 (0.44%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 446 (0.00%)	2 / 451 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 446 (0.22%)	2 / 451 (0.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			

subjects affected / exposed	0 / 446 (0.00%)	2 / 451 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 446 (0.22%)	2 / 451 (0.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 446 (0.00%)	2 / 451 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 446 (0.22%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma infection			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
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	1 / 446 (0.22%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung abscess			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis aseptic			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perirectal abscess			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pilonidal cyst			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			

subjects affected / exposed	1 / 446 (0.22%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 446 (0.22%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Subcutaneous abscess			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess			
subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	2 / 446 (0.45%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			

subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			
subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (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	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orchitis			
subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scrotal abscess			

subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	3 / 446 (0.67%)	4 / 451 (0.89%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	7 / 446 (1.57%)	3 / 451 (0.67%)	
occurrences causally related to treatment / all	4 / 7	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	5 / 446 (1.12%)	3 / 451 (0.67%)	
occurrences causally related to treatment / all	1 / 5	1 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 446 (0.00%)	2 / 451 (0.44%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 446 (0.00%)	2 / 451 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Decreased appetite			
subjects affected / exposed	2 / 446 (0.45%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cachexia			

subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 446 (0.00%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			
subjects affected / exposed	1 / 446 (0.22%)	1 / 451 (0.22%)	
occurrences causally related to treatment / all	0 / 5	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	1 / 446 (0.22%)	0 / 451 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Sunitinib	Atezolizumab + Bevacizumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	433 / 446 (97.09%)	434 / 451 (96.23%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	189 / 446 (42.38%)	168 / 451 (37.25%)	
occurrences (all)	334	257	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	103 / 446 (23.09%)	79 / 451 (17.52%)	
occurrences (all)	179	125	
Chest pain			

subjects affected / exposed	24 / 446 (5.38%)	15 / 451 (3.33%)	
occurrences (all)	24	24	
Fatigue			
subjects affected / exposed	166 / 446 (37.22%)	150 / 451 (33.26%)	
occurrences (all)	263	214	
Influenza like illness			
subjects affected / exposed	19 / 446 (4.26%)	38 / 451 (8.43%)	
occurrences (all)	22	63	
Mucosal inflammation			
subjects affected / exposed	125 / 446 (28.03%)	41 / 451 (9.09%)	
occurrences (all)	216	60	
Oedema peripheral			
subjects affected / exposed	45 / 446 (10.09%)	51 / 451 (11.31%)	
occurrences (all)	54	67	
Pain			
subjects affected / exposed	12 / 446 (2.69%)	24 / 451 (5.32%)	
occurrences (all)	12	25	
Pyrexia			
subjects affected / exposed	50 / 446 (11.21%)	69 / 451 (15.30%)	
occurrences (all)	59	92	
Respiratory, thoracic and mediastinal disorders			
Dysphonia			
subjects affected / exposed	18 / 446 (4.04%)	61 / 451 (13.53%)	
occurrences (all)	19	68	
Cough			
subjects affected / exposed	87 / 446 (19.51%)	96 / 451 (21.29%)	
occurrences (all)	104	124	
Dyspnoea			
subjects affected / exposed	43 / 446 (9.64%)	56 / 451 (12.42%)	
occurrences (all)	57	67	
Epistaxis			
subjects affected / exposed	65 / 446 (14.57%)	73 / 451 (16.19%)	
occurrences (all)	87	90	
Oropharyngeal pain			

subjects affected / exposed	16 / 446 (3.59%)	37 / 451 (8.20%)	
occurrences (all)	20	44	
Rhinorrhoea			
subjects affected / exposed	9 / 446 (2.02%)	30 / 451 (6.65%)	
occurrences (all)	9	33	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	15 / 446 (3.36%)	30 / 451 (6.65%)	
occurrences (all)	15	32	
Insomnia			
subjects affected / exposed	35 / 446 (7.85%)	35 / 451 (7.76%)	
occurrences (all)	38	37	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	34 / 446 (7.62%)	26 / 451 (5.76%)	
occurrences (all)	49	41	
Aspartate aminotransferase increased			
subjects affected / exposed	35 / 446 (7.85%)	25 / 451 (5.54%)	
occurrences (all)	48	31	
Neutrophil count decreased			
subjects affected / exposed	24 / 446 (5.38%)	3 / 451 (0.67%)	
occurrences (all)	53	3	
Blood creatinine increased			
subjects affected / exposed	36 / 446 (8.07%)	35 / 451 (7.76%)	
occurrences (all)	73	50	
Platelet count decreased			
subjects affected / exposed	46 / 446 (10.31%)	1 / 451 (0.22%)	
occurrences (all)	83	1	
Weight decreased			
subjects affected / exposed	25 / 446 (5.61%)	34 / 451 (7.54%)	
occurrences (all)	33	39	
Nervous system disorders			
Dizziness			
subjects affected / exposed	24 / 446 (5.38%)	50 / 451 (11.09%)	
occurrences (all)	30	62	
Dysgeusia			

subjects affected / exposed	128 / 446 (28.70%)	31 / 451 (6.87%)	
occurrences (all)	172	35	
Headache			
subjects affected / exposed	76 / 446 (17.04%)	99 / 451 (21.95%)	
occurrences (all)	99	145	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	91 / 446 (20.40%)	40 / 451 (8.87%)	
occurrences (all)	160	57	
Leukopenia			
subjects affected / exposed	26 / 446 (5.83%)	5 / 451 (1.11%)	
occurrences (all)	48	9	
Neutropenia			
subjects affected / exposed	55 / 446 (12.33%)	3 / 451 (0.67%)	
occurrences (all)	122	3	
Thrombocytopenia			
subjects affected / exposed	78 / 446 (17.49%)	13 / 451 (2.88%)	
occurrences (all)	165	29	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	38 / 446 (8.52%)	40 / 451 (8.87%)	
occurrences (all)	62	46	
Abdominal pain upper			
subjects affected / exposed	36 / 446 (8.07%)	16 / 451 (3.55%)	
occurrences (all)	55	17	
Constipation			
subjects affected / exposed	62 / 446 (13.90%)	79 / 451 (17.52%)	
occurrences (all)	76	95	
Diarrhoea			
subjects affected / exposed	230 / 446 (51.57%)	128 / 451 (28.38%)	
occurrences (all)	527	204	
Dry mouth			
subjects affected / exposed	25 / 446 (5.61%)	31 / 451 (6.87%)	
occurrences (all)	35	42	
Dyspepsia			

subjects affected / exposed	84 / 446 (18.83%)	28 / 451 (6.21%)	
occurrences (all)	103	34	
Gastrooesophageal reflux disease			
subjects affected / exposed	51 / 446 (11.43%)	9 / 451 (2.00%)	
occurrences (all)	59	9	
Stomatitis			
subjects affected / exposed	99 / 446 (22.20%)	45 / 451 (9.98%)	
occurrences (all)	162	56	
Toothache			
subjects affected / exposed	14 / 446 (3.14%)	25 / 451 (5.54%)	
occurrences (all)	16	33	
Vomiting			
subjects affected / exposed	111 / 446 (24.89%)	54 / 451 (11.97%)	
occurrences (all)	186	90	
Nausea			
subjects affected / exposed	167 / 446 (37.44%)	87 / 451 (19.29%)	
occurrences (all)	276	117	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	37 / 446 (8.30%)	40 / 451 (8.87%)	
occurrences (all)	41	48	
Hair colour changes			
subjects affected / exposed	31 / 446 (6.95%)	0 / 451 (0.00%)	
occurrences (all)	31	0	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	195 / 446 (43.72%)	20 / 451 (4.43%)	
occurrences (all)	407	22	
Rash			
subjects affected / exposed	66 / 446 (14.80%)	85 / 451 (18.85%)	
occurrences (all)	91	124	
Pruritus			
subjects affected / exposed	30 / 446 (6.73%)	95 / 451 (21.06%)	
occurrences (all)	34	130	
Skin discolouration			

subjects affected / exposed	28 / 446 (6.28%)	0 / 451 (0.00%)	
occurrences (all)	37	0	
Yellow skin			
subjects affected / exposed	28 / 446 (6.28%)	1 / 451 (0.22%)	
occurrences (all)	38	1	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	23 / 446 (5.16%)	12 / 451 (2.66%)	
occurrences (all)	59	23	
Proteinuria			
subjects affected / exposed	29 / 446 (6.50%)	91 / 451 (20.18%)	
occurrences (all)	39	149	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	111 / 446 (24.89%)	99 / 451 (21.95%)	
occurrences (all)	131	108	
Hyperthyroidism			
subjects affected / exposed	14 / 446 (3.14%)	32 / 451 (7.10%)	
occurrences (all)	16	33	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	56 / 446 (12.56%)	102 / 451 (22.62%)	
occurrences (all)	64	140	
Back pain			
subjects affected / exposed	55 / 446 (12.33%)	72 / 451 (15.96%)	
occurrences (all)	73	91	
Musculoskeletal pain			
subjects affected / exposed	23 / 446 (5.16%)	40 / 451 (8.87%)	
occurrences (all)	25	44	
Myalgia			
subjects affected / exposed	21 / 446 (4.71%)	57 / 451 (12.64%)	
occurrences (all)	26	64	
Pain in extremity			
subjects affected / exposed	33 / 446 (7.40%)	41 / 451 (9.09%)	
occurrences (all)	46	60	
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	32 / 446 (7.17%)	36 / 451 (7.98%)	
occurrences (all)	36	47	
Upper respiratory tract infection			
subjects affected / exposed	25 / 446 (5.61%)	33 / 451 (7.32%)	
occurrences (all)	26	49	
Urinary tract infection			
subjects affected / exposed	15 / 446 (3.36%)	24 / 451 (5.32%)	
occurrences (all)	22	33	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	142 / 446 (31.84%)	83 / 451 (18.40%)	
occurrences (all)	185	96	
Hyperkalaemia			
subjects affected / exposed	13 / 446 (2.91%)	28 / 451 (6.21%)	
occurrences (all)	19	36	
Hyponatraemia			
subjects affected / exposed	16 / 446 (3.59%)	25 / 451 (5.54%)	
occurrences (all)	20	32	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 May 2015	Amendments primarily included the following safety-related changes: information on potential risk of systemic immune activation with Atezolizumab (MPDL3280A) was added, adverse event reporting for serious adverse events (SAEs) and adverse events of special interest (AESIs_ was extended to 90 days after the last dose of Atezolizumab or Bevacizumab, and pregnancy testing was modified to reflect serial monitoring in eligible participants.
10 October 2015	The following changes were included: The management of gastrointestinal, dermatologic, endocrine, pulmonary toxicity, hepatotoxicity, potential pancreatic or eye toxicity and other immune-mediated adverse events (AEs) was updated; The management recommendations regarding early identification and management of systemic immune activation (SIA) were added; Eligibility criteria for sarcomatoid histology were broadened to allow inclusion of participants whose tumors demonstrated any component of sarcomatoid histology; Participants with treated, asymptomatic, cerebellar metastases were eligible to be enrolled provided that specific criteria were met; Eligibility for participants with malignancies other than RCC within 5 years was clarified.
10 December 2015	The following changes were included: The primary endpoint was changed from PFS alone in the ITT population to a coprimary endpoint of PFS and OS in the group of participants with IC1/2/3; The number of events required for the analyses of PFS and OS was changed and the total sample size was increased from approximately 550 to approximately 830 participants, including a minimum of approximately 457 participants in the IC1/2/3 PD-L1 expression group.
14 July 2016	The statistical analysis plan and analysis hierarchy was modified in order to maintain adequate power for the co-primary endpoints.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The reported results include data collected up to the clinical data cut-off date of 29 September 2017.

Notes: