



Clinical trial results:

A Phase III, Open-label, Randomized Study of Atezolizumab in Combination With Bevacizumab Compared With sorafenib in Patients With Untreated Locally Advanced or Metastatic Hepatocellular Carcinoma

Summary

EudraCT number	2017-003691-31
Trial protocol	PL DE GB CZ ES IT
Global end of trial date	

Results information

Result version number	v1
This version publication date	01 September 2021
First version publication date	01 September 2021

Trial information

Trial identification

Sponsor protocol code	YO40245
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03434379
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	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, 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	31 August 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 August 2020
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study is to evaluate the efficacy and safety of atezolizumab in combination with bevacizumab compared with sorafenib in participants with locally advanced or metastatic Hepatocellular Carcinoma (HCC) who had received no prior systemic treatment.

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 March 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	3 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 9
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	China: 135
Country: Number of subjects enrolled	Czechia: 5
Country: Number of subjects enrolled	Germany: 16
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	France: 42
Country: Number of subjects enrolled	United Kingdom: 13
Country: Number of subjects enrolled	Hong Kong: 18
Country: Number of subjects enrolled	Italy: 17
Country: Number of subjects enrolled	Japan: 61
Country: Number of subjects enrolled	Korea, Republic of: 47
Country: Number of subjects enrolled	Poland: 23
Country: Number of subjects enrolled	Russian Federation: 24
Country: Number of subjects enrolled	Singapore: 17
Country: Number of subjects enrolled	Taiwan: 41
Country: Number of subjects enrolled	United States: 74
Worldwide total number of subjects	558
EEA total number of subjects	114

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)	300
From 65 to 84 years	250
85 years and over	8

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at 117 sites in 17 countries: Australia, Canada, China, Czech Republic, Germany, Spain, France, United Kingdom, Hong Kong, Italy, Japan, Republic of Korea, Poland, Russian Federation, Singapore, Taiwan, United States.

Pre-assignment

Screening details:

The study included 558 participants with 501 in the Global population. An additional 57 participants enrolled during the China Extension. The total China population included 137 Chinese participants from the Global population plus 57 participants from the China extension. The Global population and the China population were analysed separately.

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Sorafenib - Global

Arm description:

Participants in the Global population received sorafenib until unacceptable toxicity or loss of clinical benefit as determined by the investigator.

Arm type	Active comparator
Investigational medicinal product name	Sorafenib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Sorafenib was administered by mouth, 400 mg twice per day, on Days 1-21 of each 21-day cycle.

Arm title	Atezolizumab + Bevacizumab - Global
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Arm description:

Participants in the Global population received Atezolizumab + Bevacizumab until unacceptable toxicity or loss of clinical benefit as determined by the investigator.

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

Dosage and administration details:

Bevacizumab was administered by IV, 15 mg/kg on Day 1 of each 21- day cycle.

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

Dosage and administration details:

Atezolizumab was administered by IV, 1200 mg on Day 1 of each 21-day cycle.

Arm title	Sorafenib - China
Arm description:	
Participants in the China population received sorafenib until unacceptable toxicity or loss of clinical benefit as determined by the investigator.	
Arm type	Active comparator
Investigational medicinal product name	Sorafenib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Sorafenib was administered by mouth, 400 mg twice per day, on Days 1-21 of each 21-day cycle.	

Arm title	Atezolizumab + Bevacizumab - China
Arm description:	
Participants in the China population received Atezolizumab + Bevacizumab until unacceptable toxicity or loss of clinical benefit as determined by the investigator.	
Arm type	Experimental
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Bevacizumab was administered by IV, 15 mg/kg on Day 1 of each 21- day cycle.	
Investigational medicinal product name	Atezolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Atezolizumab was administered by IV, 1200 mg on Day 1 of each 21-day cycle.	

Number of subjects in period 1	Sorafenib - Global	Atezolizumab + Bevacizumab - Global	Sorafenib - China
Started	165	336	61
Completed	0	0	0
Not completed	165	336	61
Adverse event, serious fatal	99	179	38
Consent withdrawn by subject	20	20	7
Lost to follow-up	3	1	1
On Study	43	136	15

Number of subjects in period 1	Atezolizumab + Bevacizumab - China
Started	133
Completed	0
Not completed	133

Adverse event, serious fatal	61
Consent withdrawn by subject	6
Lost to follow-up	-
On Study	66

Baseline characteristics

Reporting groups

Reporting group title	Overall Period
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Reporting group description: -

Reporting group values	Overall Period	Total	
Number of subjects	558	558	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	300	300	
From 65-84 years	250	250	
85 years and over	8	8	
Sex/Gender, Customized			
Global population			
Units: participants			
Female	92	92	
Male	466	466	

End points

End points reporting groups

Reporting group title	Sorafenib - Global
Reporting group description: Participants in the Global population received sorafenib until unacceptable toxicity or loss of clinical benefit as determined by the investigator.	
Reporting group title	Atezolizumab + Bevacizumab - Global
Reporting group description: Participants in the Global population received Atezolizumab + Bevacizumab until unacceptable toxicity or loss of clinical benefit as determined by the investigator.	
Reporting group title	Sorafenib - China
Reporting group description: Participants in the China population received sorafenib until unacceptable toxicity or loss of clinical benefit as determined by the investigator.	
Reporting group title	Atezolizumab + Bevacizumab - China
Reporting group description: Participants in the China population received Atezolizumab + Bevacizumab until unacceptable toxicity or loss of clinical benefit as determined by the investigator.	

Primary: Overall Survival (OS) in the Global Population

End point title	Overall Survival (OS) in the Global Population ^[1]
End point description: OS was defined as the time from randomization to death from any cause. Global ITT population consisted of all randomized participants in the Global population, whether or not the participant had received the assigned study treatment. 9999/99999 = not estimable due to the limited number of events observed	
End point type	Primary
End point timeframe: From randomization to death from any cause up to the clinical cut off date (CCOD) of 29Aug2019 (up to approximately 18 months) and 31Aug2020 (up to approximately 30 months)	

Notes:

[1] - 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: This endpoint only reports the data for the Global population.

End point values	Sorafenib - Global	Atezolizumab + Bevacizumab - Global		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	336		
Units: months				
median (confidence interval 95%)				
At CCOD 18 months	13.24 (10.41 to 99999)	9999 (9999 to 99999)		
At CCOD 30 months	13.40 (11.37 to 16.85)	19.22 (17.02 to 23.66)		

Statistical analyses

Statistical analysis title	OS at CCOD 18 months- Global
Statistical analysis description:	
Stratified by geographic region (Asia [excluding Japan] vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline alpha-fetoprotein (AFP: <400 vs. ≥ 400 ng/mL).	
Comparison groups	Sorafenib - Global v Atezolizumab + Bevacizumab - Global
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0006
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	0.79

Statistical analysis title	OS at CCOD 30 months - Global
Statistical analysis description:	
Stratified by geographic region (Asia [excluding Japan] vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline alpha-fetoprotein (AFP: <400 vs. ≥ 400 ng/mL).	
Comparison groups	Sorafenib - Global v Atezolizumab + Bevacizumab - Global
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0009
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	0.85

Primary: Progression Free Survival by Independent Review Facility-Assessment (PFS-IRF) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 in the Global Population

End point title	Progression Free Survival by Independent Review Facility-Assessment (PFS-IRF) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 in the Global Population ^[2]
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End point description:

PFS was defined as the time from randomization to the first occurrence of progressive disease (PD) or death from any cause whichever occurs first as determined by an IRF according to RECIST v1.1. PD: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of

diameters on study (including baseline). In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 millimeters (mm). Global ITT population consisted of all randomized participants in the Global population, whether or not the participant had received the assigned study treatment.

End point type	Primary
End point timeframe:	
Randomization to the first occurrence of disease progression or death from any cause up to CCOD of 29Aug2019 (up to approximately 18 months)	

Notes:

[2] - 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: This endpoint only reports the data for the Global population.

End point values	Sorafenib - Global	Atezolizumab + Bevacizumab - Global		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	336		
Units: months				
median (confidence interval 95%)	4.27 (3.98 to 5.55)	6.83 (5.75 to 8.28)		

Statistical analyses

Statistical analysis title	PFS-IRF RECIST v1.1 - Global
Statistical analysis description:	
Stratified by geographic region (Asia [excluding Japan] vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline AFP (<400 vs. ≥ 400 ng/mL).	
Comparison groups	Sorafenib - Global v Atezolizumab + Bevacizumab - Global
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	0.76

Primary: Overall Survival (OS) in the China Population

End point title	Overall Survival (OS) in the China Population ^[3]
End point description:	
OS was defined as the time from randomization to death from any cause. China ITT population consisted of all randomized participants in the China population, whether or not the participant had received the assigned study treatment. 9999/99999 = not estimable due to the limited number of events observed	
End point type	Primary

End point timeframe:

From randomization to death from any cause up to the clinical cut off date (CCOD) of 29Aug2019 (up to approximately 18 months) and 31Aug2020 (up to approximately 30 months)

Notes:

[3] - 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: This endpoint only reports the data for the China population.

End point values	Sorafenib - China	Atezolizumab + Bevacizumab - China		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	133		
Units: months				
median (confidence interval 95%)				
At CCOD 18 months	11.37 (6.74 to 99999)	9999 (13.50 to 99999)		
At CCOD 30 months	11.37 (6.74 to 16.07)	24.05 (17.12 to 99999)		

Statistical analyses

Statistical analysis title	OS at CCOD 18 months - China
Statistical analysis description:	
Stratified by macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline AFP (<400 vs. >= 400 ng/mL).	
Comparison groups	Sorafenib - China v Atezolizumab + Bevacizumab - China
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0026
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.25
upper limit	0.76

Statistical analysis title	OS at CCOD 30 months - China
Statistical analysis description:	
Stratified by macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline AFP (<400 vs. >= 400 ng/mL).	
Comparison groups	Sorafenib - China v Atezolizumab + Bevacizumab - China

Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0019
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	0.8

Primary: PFS-IRF per RECIST v1.1 in the China Population

End point title	PFS-IRF per RECIST v1.1 in the China Population ^[4]
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End point description:

PFS was defined as the time from randomization to the first occurrence of progressive disease (PD) or death from any cause whichever occurs first as determined by an IRF according to RECIST v1.1. PD: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters on study (including baseline). In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 millimeters (mm). China ITT population consisted of all randomized participants in the China population, whether or not the participant had received the assigned study treatment.

End point type	Primary
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End point timeframe:

Randomization to the first occurrence of disease progression or death from any cause up to CCOD of 29Aug2019 (up to approximately 18 months)

Notes:

[4] - 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: This endpoint only reports the data for the China population.

End point values	Sorafenib - China	Atezolizumab + Bevacizumab - China		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	133		
Units: months				
median (confidence interval 95%)	3.19 (2.56 to 4.76)	5.72 (4.17 to 8.28)		

Statistical analyses

Statistical analysis title	PFS-IRF RECIST v1.1 - China
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Statistical analysis description:

Stratified by macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline AFP (<400 vs. ≥ 400 ng/mL).

Comparison groups	Sorafenib - China v Atezolizumab + Bevacizumab - China
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Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0117
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	0.9

Secondary: Objective Response Rate by IRF-Assessment (ORR-IRF) per RECIST v1.1 in the Global Population

End point title	Objective Response Rate by IRF-Assessment (ORR-IRF) per RECIST v1.1 in the Global Population ^[5]
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End point description:

ORR was defined as the percentage of participants with a complete response (CR) or a partial response (PR) as determined by the IRF according to RECIST v1.1. CR: disappearance of all target lesions. PR: At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR. OR=CR+PR Global ITT population with measurable disease at baseline consisted of all randomized participants in the Global population, whether or not the participant had received the assigned study treatment, and had measurable disease at baseline.

End point type	Secondary
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End point timeframe:

Randomization up to CCOD of 29Aug2019 (up to approximately 18 months)

Notes:

[5] - 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: This endpoint only reports the data for the Global population.

End point values	Sorafenib - Global	Atezolizumab + Bevacizumab - Global		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	326		
Units: percentage of participants				
number (confidence interval 95%)	11.9 (7.35 to 18.03)	27.3 (22.54 to 32.48)		

Statistical analyses

Statistical analysis title	ORR-IRF RECIST v1.1 - Global
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Statistical analysis description:

Stratified by geographic region (Asia [excluding Japan] vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline AFP (<400 vs. ≥ 400 ng/mL).

Comparison groups	Sorafenib - Global v Atezolizumab + Bevacizumab - Global
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Number of subjects included in analysis	485
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.68
upper limit	5.01

Secondary: Objective Response Rate by IRF-Assessment (ORR-IRF) per Hepatocellular Carcinoma (HCC) modified RECIST (mRECIST) in the Global Population

End point title	Objective Response Rate by IRF-Assessment (ORR-IRF) per Hepatocellular Carcinoma (HCC) modified RECIST (mRECIST) in the Global Population ^[6]
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End point description:

ORR was defined as the percentage of participants with CR or PR as determined by the IRF according to HCC mRECIST. HCC mRECIST differentiates between vital tumor and necrotic areas in the liver measuring only the residual vital tumor mass in the liver. CR: disappearance of all target lesions. PR: At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR. OR=CR+PR Global ITT population with measurable disease at baseline consisted of all randomized participants in the Global population, whether or not the participant had received the assigned study treatment, and had measurable disease at baseline.

End point type	Secondary
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End point timeframe:

Randomization up to CCOD of 29Aug2019 (up to approximately 18 months)

Notes:

[6] - 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: This endpoint only reports the data for the Global population.

End point values	Sorafenib - Global	Atezolizumab + Bevacizumab - Global		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	158	325		
Units: percentage of participants				
number (confidence interval 95%)	13.3 (8.42 to 19.60)	33.2 (28.13 to 38.64)		

Statistical analyses

Statistical analysis title	ORR-IRF HCC mRECIST - Global
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Statistical analysis description:

Stratified by geographic region (Asia [excluding Japan] vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline AFP (<400 vs. ≥ 400 ng/mL).

Comparison groups	Sorafenib - Global v Atezolizumab + Bevacizumab - Global
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Number of subjects included in analysis	483
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	3.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.02
upper limit	5.71

Secondary: ORR by Investigator-Assessment (ORR-INV) per RECIST v1.1 in the Global Population

End point title	ORR by Investigator-Assessment (ORR-INV) per RECIST v1.1 in the Global Population ^[7]
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End point description:

ORR was defined as the percentage of participants with CR or PR as determined by the investigator according to RECIST v1.1. CR: disappearance of all target lesions. PR: At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR. OR=CR+PR Global ITT population with measurable disease at baseline consisted of all randomized participants in the Global population, whether or not the participant had received the assigned study treatment, and had measurable disease at baseline.

End point type	Secondary
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End point timeframe:

Randomization up to CCOD of 29Aug2019 (up to approximately 18 months)

Notes:

[7] - 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: This endpoint only reports the data for the Global population.

End point values	Sorafenib - Global	Atezolizumab + Bevacizumab - Global		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	336		
Units: percentage of participants				
number (confidence interval 95%)	5.5 (2.54 to 10.16)	25.6 (21.01 to 30.61)		

Statistical analyses

Statistical analysis title	ORR-INV RECIST v1.1 - Global
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Statistical analysis description:

Stratified by geographic region (Asia [excluding Japan] vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline AFP (<400 vs. ≥ 400 ng/mL).

Comparison groups	Sorafenib - Global v Atezolizumab + Bevacizumab - Global
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Number of subjects included in analysis	500
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	6.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.99
upper limit	12.66

Secondary: Duration of Response by IRF-Assessment (DOR-IRF) per RECIST v1.1 in the Global Population

End point title	Duration of Response by IRF-Assessment (DOR-IRF) per RECIST v1.1 in the Global Population ^[8]
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End point description:

DOR was defined as the time interval from the date of first occurrence of a documented objective response (CR or PR, whichever status is recorded first) until the first date that disease progression (PD) or death was documented, whichever occurs first as determined by the IRF according to RECIST v1.1. CR: disappearance of all target lesions. PR: At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR. PD: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters on study (including baseline). In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 mm. The analysis population included Global participants with a confirmed response (CR or PR). 9999/99999 = not estimable due to the limited number of events observed

End point type	Secondary
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End point timeframe:

Randomization up to CCOD of 29Aug2019 (up to approximately 18 months)

Notes:

[8] - 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: This endpoint only reports the data for the Global population.

End point values	Sorafenib - Global	Atezolizumab + Bevacizumab - Global		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	89		
Units: months				
median (confidence interval 95%)	6.28 (4.67 to 99999)	9999 (9999 to 99999)		

Statistical analyses

Statistical analysis title	DOR-IRF RECIST v1.1 - Global
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Statistical analysis description:

Stratified by geographic region (Asia [excluding Japan] vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline AFP (<400 vs. ≥ 400 ng/mL).

Comparison groups	Sorafenib - Global v Atezolizumab + Bevacizumab - Global
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0051
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.08
upper limit	0.7

Secondary: Duration of Response by IRF Assessment (DOR-IRF) per HCC mRECIST in the Global Population

End point title	Duration of Response by IRF Assessment (DOR-IRF) per HCC mRECIST in the Global Population ^[9]
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End point description:

DOR: the time interval from the date of first occurrence of a documented objective response (CR or PR, whichever status is recorded first) until the first date that disease progression (PD) or death was documented, whichever occurs first as determined by the IRF according to HCC mRECIST. HCC mRECIST differentiates between vital tumor and necrotic areas in the liver, measuring only the residual vital tumor mass in the liver CR: disappearance of all target lesions. PR: At least 30% decrease in the sum of diameters of all target lesions compared to baseline, in the absence of CR. PD: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters on study (including baseline). In addition, the sum of diameters must also demonstrate an absolute increase of ≥ 5 mm. The analysis population included Global participants with a confirmed response (CR or PR). 9999/99999 = not estimable due to the limited number of events observed

End point type	Secondary
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End point timeframe:

Randomization up to CCOD of 29Aug2019 (up to approximately 18 months)

Notes:

[9] - 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: This endpoint only reports the data for the Global population.

End point values	Sorafenib - Global	Atezolizumab + Bevacizumab - Global		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	108		
Units: months				
median (confidence interval 95%)	6.28 (4.86 to 99999)	9999 (9999 to 99999)		

Statistical analyses

Statistical analysis title	DOR-IRF HCC mRECIST - Global
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Statistical analysis description:

Stratified by geographic region (Asia [excluding Japan] vs. rest of world), macrovascular invasion and/or

extrahepatic spread (presence vs. absence), and baseline AFP (<400 vs. \geq 400 ng/mL).

Comparison groups	Sorafenib - Global v Atezolizumab + Bevacizumab - Global
Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0048
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.12
upper limit	0.73

Secondary: Duration of Response by Investigator Assessment (DOR-INV) per RECIST v1.1 in the Global Population

End point title	Duration of Response by Investigator Assessment (DOR-INV) per RECIST v1.1 in the Global Population ^[10]
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End point description:

DOR was defined as the time interval from the date of first occurrence of a documented objective response (CR or PR, whichever status is recorded first) until the first date that disease progression (PD) or death was documented, whichever occurs first as determined by the investigator according to RECIST v1.1. CR: disappearance of all target lesions. PR: At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR. PD: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters on study (including baseline). In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of \geq 5 mm. The analysis population included Global participants with a confirmed response (CR or PR). 9999/99999 = not estimable due to the limited number of events observed

End point type	Secondary
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End point timeframe:

Randomization up to CCOD of 29Aug2019 (up to approximately 18 months)

Notes:

[10] - 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: This endpoint only reports the data for the Global population.

End point values	Sorafenib - Global	Atezolizumab + Bevacizumab - Global		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	86		
Units: months				
median (confidence interval 95%)	9999 (5.39 to 99999)	13.08 (13.08 to 99999)		

Statistical analyses

Statistical analysis title	DOR-INV RECIST v1.1 - Global
Statistical analysis description:	
Stratified by geographic region (Asia [excluding Japan] vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline AFP (<400 vs. \geq 400 ng/mL).	
Comparison groups	Sorafenib - Global v Atezolizumab + Bevacizumab - Global
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4187
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.16
upper limit	2.15

Secondary: PFS-IRF per HCC mRECIST in the Global Population

End point title	PFS-IRF per HCC mRECIST in the Global Population ^[11]
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End point description:

PFS was defined as the time from randomization to the first occurrence of progressive disease or death from any cause whichever occurs first as determined by the IRF according to HCC mRECIST. HCC mRECIST differentiates between vital tumor and necrotic areas in the liver, measuring only the residual vital tumor mass in the liver. PD: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters on study (including baseline). In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of \geq 5 millimeters (mm). Global ITT population consisted of all randomized participants in the Global population, whether or not the participant had received the assigned study treatment.

End point type	Secondary
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End point timeframe:

Randomization to the first occurrence of disease progression or death from any cause up to CCOD of 29Aug2019 (up to approximately 18 months)

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint only reports the data for the Global population.

End point values	Sorafenib - Global	Atezolizumab + Bevacizumab - Global		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	336		
Units: months				
median (confidence interval 95%)	4.24 (3.98 to 5.45)	6.83 (5.72 to 7.69)		

Statistical analyses

Statistical analysis title	PFS-IRF HCC mRECIST - Global
Statistical analysis description:	
Stratified by geographic region (Asia [excluding Japan] vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline AFP (<400 vs. ≥ 400 ng/mL).	
Comparison groups	Sorafenib - Global v Atezolizumab + Bevacizumab - Global
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	0.74

Secondary: PFS by Investigator Assessment (PFS-INV) per RECIST v1.1 in the Global Population

End point title	PFS by Investigator Assessment (PFS-INV) per RECIST v1.1 in the Global Population ^[12]
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End point description:

PFS was defined as the time from randomization to the first occurrence of progressive disease or death from any cause whichever occurs first as determined by the investigator according to RECIST v1.1. PD: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters on study (including baseline). In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 millimeters (mm). Global ITT population consisted of all randomized participants in the Global population, whether or not the participant had received the assigned study treatment.

End point type	Secondary
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End point timeframe:

Randomization to the first occurrence of disease progression or death from any cause up to CCOD of 29Aug2019 (up to approximately 18 months)

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint only reports the data for the Global population.

End point values	Sorafenib - Global	Atezolizumab + Bevacizumab - Global		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	336		
Units: months				
median (confidence interval 95%)	2.89 (2.76 to 4.17)	7.06 (5.68 to 8.44)		

Statistical analyses

Statistical analysis title	PFS-INV RECIST v1.1 - Global
Statistical analysis description: Stratified by geographic region (Asia [excluding Japan] vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline AFP (<400 vs. ≥ 400 ng/mL).	
Comparison groups	Sorafenib - Global v Atezolizumab + Bevacizumab - Global
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	0.57

Secondary: Time to Progression (TTP) by IRF Assessment (TTP-IRF) per RECIST v1.1 in the Global Population

End point title	Time to Progression (TTP) by IRF Assessment (TTP-IRF) per RECIST v1.1 in the Global Population ^[13]
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End point description:

Time to progression was defined as the time from the date of randomization to the date of the first documented tumor progression as determined by the IRF according to RECIST v1.1. PD: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters on study (including baseline). In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 millimeters (mm). Global ITT population consisted of all randomized participants in the Global population, whether or not the participant had received the assigned study treatment.

End point type	Secondary
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End point timeframe:

Randomization to the first occurrence of disease progression or death from any cause up to CCOD of 29Aug2019 (up to approximately 18 months)

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint only reports the data for the Global population.

End point values	Sorafenib - Global	Atezolizumab + Bevacizumab - Global		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	336		
Units: months				
median (confidence interval 95%)	5.59 (4.21 to 7.72)	8.57 (6.83 to 9.86)		

Statistical analyses

Statistical analysis title	TTP-IRF RECIST v1.1 - Global
Statistical analysis description:	
Stratified by geographic region (Asia [excluding Japan] vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline AFP (<400 vs. \geq 400 ng/mL).	
Comparison groups	Sorafenib - Global v Atezolizumab + Bevacizumab - Global
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0105
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	0.92

Secondary: TTP-IRF per HCC mRECIST in the Global Population

End point title	TTP-IRF per HCC mRECIST in the Global Population ^[14]
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End point description:

Time to progression was defined as the time from the date of randomization to the date of the first documented tumor progression as determined by the IRF according to HCC mRECIST. HCC mRECIST differentiates between vital tumor and necrotic areas in the liver, measuring only the residual vital tumor mass in the liver. PD: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters on study (including baseline). In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of \geq 5 millimeters (mm). Global ITT population consisted of all randomized participants in the Global population, whether or not the participant had received the assigned study treatment.

End point type	Secondary
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End point timeframe:

Randomization to the first occurrence of disease progression or death from any cause up to CCOD of 29Aug2019 (up to approximately 18 months)

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint only reports the data for the Global population.

End point values	Sorafenib - Global	Atezolizumab + Bevacizumab - Global		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	336		
Units: months				
median (confidence interval 95%)	5.55 (4.21 to 7.69)	8.28 (6.80 to 9.86)		

Statistical analyses

Statistical analysis title	TTP-IRF HCC mRECIST - Global
Statistical analysis description: Stratified by geographic region (Asia [excluding Japan] vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline AFP (<400 vs. \geq 400 ng/mL).	
Comparison groups	Sorafenib - Global v Atezolizumab + Bevacizumab - Global
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0063
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	0.9

Secondary: TTP by Investigator Assessment (TTP-INV) per RECIST v1.1 in the Global Population

End point title	TTP by Investigator Assessment (TTP-INV) per RECIST v1.1 in the Global Population ^[15]
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End point description:

Time to progression was defined as the time from the date of randomization to the date of the first documented tumor progression as determined by the investigator according to RECIST v1.1. PD: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters on study (including baseline). In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of \geq 5 millimeters (mm). Global ITT population consisted of all randomized participants in the Global population, whether or not the participant had received the assigned study treatment.

End point type	Secondary
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End point timeframe:

Randomization to the first occurrence of disease progression or death from any cause up to CCOD of 29Aug2019 (up to approximately 18 months)

Notes:

[15] - 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: This endpoint only reports the data for the Global population.

End point values	Sorafenib - Global	Atezolizumab + Bevacizumab - Global		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	336		
Units: months				
median (confidence interval 95%)	3.98 (2.83 to 4.30)	8.54 (6.93 to 9.92)		

Statistical analyses

Statistical analysis title	TTP-INV RECIST v1.1 - Global
Statistical analysis description:	
Stratified by geographic region (Asia [excluding Japan] vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline AFP (<400 vs. ≥ 400 ng/mL).	
Comparison groups	Sorafenib - Global v Atezolizumab + Bevacizumab - Global
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	0.57

Secondary: Overall Survival by Baseline AFP in the Global Population

End point title	Overall Survival by Baseline AFP in the Global Population ^[16]
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End point description:

OS was defined as the time from randomization to death from any cause. Global ITT population consisted of all randomized participants in the Global population, whether or not the participant had received the assigned study treatment. Subpopulations with baseline AFP <400 ng/mL and AFP ≥ 400 ng/mL were analyzed. 9999/99999 = not estimable due to the limited number of events observed

End point type	Secondary
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End point timeframe:

From randomization to death from any cause up to CCOD of 29Aug2019 (up to approximately 18 months)

Notes:

[16] - 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: This endpoint only reports the data for the Global population.

End point values	Sorafenib - Global	Atezolizumab + Bevacizumab - Global		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	336		
Units: months				
arithmetic mean (confidence interval 95%)				
AFP <400 ng/mL; n=104, 210	13.93 (11.73 to 99999)	9999 (9999 to 99999)		
AFP ≥400 ng/mL; n=61, 126	9.10 (5.75 to 99999)	12.78 (10.15 to 99999)		

Statistical analyses

Statistical analysis title	OS AFP <400 ng/mL - Global
Statistical analysis description: AFP <400 ng/mL and stratified by geographic region (Asia [excluding Japan] vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence).	
Comparison groups	Sorafenib - Global v Atezolizumab + Bevacizumab - Global
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0019
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.32
upper limit	0.78

Statistical analysis title	OS AFP >=400 ng/mL - Global
Statistical analysis description: AFP >= 400 ng/mL and stratified by geographic region (Asia [excluding Japan] vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence).	
Comparison groups	Sorafenib - Global v Atezolizumab + Bevacizumab - Global
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0879
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	1.06

Secondary: PFS-IRF per RECIST v1.1 by Baseline AFP in the Global Population

End point title	PFS-IRF per RECIST v1.1 by Baseline AFP in the Global Population ^[17]
End point description: PFS was defined as the time from randomization to the first occurrence of progressive disease or death from any cause whichever occurs first as determined by the IRF according to RECIST v1.1. PD: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters on study (including baseline). In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of >= 5 millimeters (mm). Global ITT population consisted of all randomized participants in the Global population, whether or not the participant had received the assigned study treatment. Subpopulations with baseline AFP <400 ng/mL and AFP>= 400 ng/mL were analyzed.	
End point type	Secondary

End point timeframe:

Randomization to the first occurrence of disease progression or death from any cause up to CCOD of 29Aug2019 (up to approximately 18 months)

Notes:

[17] - 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: This endpoint only reports the data for the Global population.

End point values	Sorafenib - Global	Atezolizumab + Bevacizumab - Global		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	336		
Units: months				
median (confidence interval 95%)				
AFP <400 ng/mL; n=104, 210	4.40 (4.01 to 6.21)	8.28 (6.83 to 11.04)		
AFP ≥400 ng/mL; n=61, 126	4.14 (2.76 to 5.26)	5.19 (3.94 to 6.77)		

Statistical analyses

Statistical analysis title	PFS-IRF RECIST v1,1 AFP≥400 ng/mL - Global
Statistical analysis description:	
AFP ≥400 ng/mL and stratified by geographic region (Asia [excluding Japan] vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence).	
Comparison groups	Sorafenib - Global v Atezolizumab + Bevacizumab - Global
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2159
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	1.15

Statistical analysis title	PFS-IRF RECIST v1,1 AFP<400 ng/mL - Global
Statistical analysis description:	
AFP<400 ng/mL and stratified by geographic region (Asia [excluding Japan] vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence).	
Comparison groups	Sorafenib - Global v Atezolizumab + Bevacizumab - Global

Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.37
upper limit	0.68

Secondary: PFS-INV per RECIST v1.1 by Baseline AFP in the Global Population

End point title	PFS-INV per RECIST v1.1 by Baseline AFP in the Global Population ^[18]
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End point description:

PFS was defined as the time from randomization to the first occurrence of progressive disease or death from any cause whichever occurs first as determined by the investigator according to RECIST v1.1. PD: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters on study (including baseline). In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 millimeters (mm). Global ITT population consisted of all randomized participants in the Global population, whether or not the participant had received the assigned study treatment. Subpopulations with baseline AFP <400 ng/mL and AFP ≥ 400 ng/mL were analyzed.

End point type	Secondary
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End point timeframe:

Randomization to the first occurrence of disease progression or death from any cause up to CCOD of 29Aug2019 (up to approximately 18 months)

Notes:

[18] - 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: This endpoint only reports the data for the Global population.

End point values	Sorafenib - Global	Atezolizumab + Bevacizumab - Global		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	336		
Units: months				
median (confidence interval 95%)				
AFP <400 ng/mL; n=104, 210	3.98 (2.79 to 5.62)	8.41 (7.06 to 9.66)		
AFP ≥ 400 ng/mL; n=61, 126	2.79 (1.58 to 3.98)	5.42 (4.17 to 6.90)		

Statistical analyses

Statistical analysis title	PFS-INV RECIST v1.1 AFP ≥ 400 ng/mL - Global
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Statistical analysis description:

AFP ≥ 400 ng/mL and stratified by geographic region (Asia [excluding Japan] vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence).

Comparison groups	Sorafenib - Global v Atezolizumab + Bevacizumab - Global
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	0.73

Statistical analysis title

PFS-INV RECIST v1.1 AFP<400 ng/mL - Global

Statistical analysis description:

AFP <400 ng/mL and stratified by geographic region (Asia [excluding Japan] vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence).

Comparison groups	Sorafenib - Global v Atezolizumab + Bevacizumab - Global
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.31
upper limit	0.57

Secondary: Time to Deterioration (TTD) in the Global Population

End point title	Time to Deterioration (TTD) in the Global Population ^[19]
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End point description:

TTD was defined as the time from randomization to the first deterioration (decrease from baseline of ≥ 10 points) in the patient-reported health-related global health status/quality of life (GHS /HRQoL), physical function or role function scales of the European Organization for Research and Treatment of Cancer quality-of-life questionnaire for cancer (EORTC) QLQ-C30, maintained for two consecutive assessments, or one assessment followed by death from any cause within 3 weeks. Global ITT population consisted of all randomized participants in the Global population, whether or not the participant had received the assigned study treatment. 99999 = not estimable due to the limited number of events observed

End point type	Secondary
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End point timeframe:

Randomization to the first occurrence of disease progression or death from any cause up to CCOD of

Notes:

[19] - 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: This endpoint only reports the data for the Global population.

End point values	Sorafenib - Global	Atezolizumab + Bevacizumab - Global		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	336		
Units: months				
median (confidence interval 95%)				
Physical Functioning	4.86 (3.48 to 6.24)	13.14 (9.69 to 99999)		
Role Functioning	3.58 (2.20 to 5.98)	9.13 (6.51 to 99999)		
GHS/QoL	3.58 (3.02 to 6.97)	11.24 (5.98 to 99999)		

Statistical analyses

Statistical analysis title	TTD Physical Functioning - Global
Statistical analysis description:	
Physical Functioning: Stratified by geographic region (Asia [excluding Japan] vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline AFP (<400 vs. ≥ 400 ng/mL).	
Comparison groups	Sorafenib - Global v Atezolizumab + Bevacizumab - Global
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	0.73

Statistical analysis title	TTD Role Functioning - Global
Statistical analysis description:	
Role Functioning: Stratified by geographic region (Asia [excluding Japan] vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline AFP (<400 vs. ≥ 400 ng/mL).	
Comparison groups	Sorafenib - Global v Atezolizumab + Bevacizumab - Global

Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0019
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	0.84

Statistical analysis title	TTD GHS/QoL - Global
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Statistical analysis description:

GHS/QoL: Stratified by geographic region (Asia [excluding Japan] vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline AFP (<400 vs. ≥ 400 ng/mL).

Comparison groups	Sorafenib - Global v Atezolizumab + Bevacizumab - Global
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0028
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	0.85

Secondary: Percentage of Participants With Adverse Events (AEs) in the Global Population

End point title	Percentage of Participants With Adverse Events (AEs) in the Global Population ^[20]
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End point description:

An adverse event is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered as adverse events. Global safety population included all randomized Global participants who received any amount of study drug with participants grouped according to the treatment the participant actually received.

End point type	Secondary
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End point timeframe:

Up to end of study (up to approximately 40 months)

Notes:

[20] - 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: This endpoint will report the data for the Global population after study completion.

End point values	Sorafenib - Global	Atezolizumab + Bevacizumab - Global		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[21]	0 ^[22]		
Units: percentage of participants				

Notes:

[21] - To be reported at end of study

[22] - To be reported at end of study

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Serum Concentration (Cmax) of Atezolizumab at Cycle 1 in the Global Population

End point title	Maximum Serum Concentration (Cmax) of Atezolizumab at Cycle 1 in the Global Population ^[23]
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End point description:

The pharmacokinetic (PK)-evaluable population was defined as all participants in the Global population who received any dose of study treatment and who had at least one post-baseline PK sample available.

End point type	Secondary
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End point timeframe:

Post-dose on Day 1 of Cycle 1

Notes:

[23] - 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: This endpoint only reports the data for the Global population treated with atezolizumab.

End point values	Atezolizumab + Bevacizumab - Global			
Subject group type	Reporting group			
Number of subjects analysed	309			
Units: micrograms/milliliter (mcg/mL)				
arithmetic mean (standard deviation)	398 (± 132)			

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Serum Concentration (Cmin) of Atezolizumab in the Global Population

End point title	Trough Serum Concentration (Cmin) of Atezolizumab in the Global Population ^[24]
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End point description:

The pharmacokinetic (PK)-evaluable population was defined as all participants in the Global population who received any dose of study treatment and who had at least one post-baseline PK sample available.

End point type	Secondary
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End point timeframe:

Pre-dose on Day 1 of Cycles 2, 3, 4, 8, 12 and 16

Notes:

[24] - 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: This endpoint only reports the data for the Global population treated with atezolizumab.

End point values	Atezolizumab + Bevacizumab - Global			
Subject group type	Reporting group			
Number of subjects analysed	329			
Units: mcg/mL				
arithmetic mean (standard deviation)				
Pre-dose Cycle 2, Day 1; n=298	79.2 (± 50.2)			
Pre-dose Cycle 3, Day 1; n=41	101 (± 55.4)			
Pre-dose Cycle 4, Day 1; n=263	131 (± 63.7)			
Pre-dose Cycle 8, Day 1; n=134	145 (± 61.7)			
Pre-dose Cycle 12, Day 1; n=153	168 (± 82.9)			
Pre-dose Cycle 16, Day 1; n=124	167 (± 65.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Anti-Drug Antibodies (ADAs) to Atezolizumab in the Global Population

End point title	Percentage of Participants With Anti-Drug Antibodies (ADAs) to Atezolizumab in the Global Population ^[25]
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End point description:

The Global ADA-evaluable population was defined as all participants in the Global population who received any dose of atezolizumab and who had at least one post-baseline ADA assessment.

End point type	Secondary
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End point timeframe:

Up to CCOD of 31Aug2020 (up to approximately 30 months)

Notes:

[25] - 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: This endpoint only reports the data for the Global population treated with atezolizumab.

End point values	Atezolizumab + Bevacizumab - Global			
Subject group type	Reporting group			
Number of subjects analysed	329			
Units: percentage of participants				
number (not applicable)				
Baseline; n=316	2.2			
Post-baseline; n=318	29.6			

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate by IRF-Assessment (ORR-IRF) per RECIST v1.1 in the China Population

End point title	Objective Response Rate by IRF-Assessment (ORR-IRF) per RECIST v1.1 in the China Population ^[26]
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End point description:

ORR was defined as the percentage of participants with a complete response (CR) or a partial response (PR) as determined by the IRF according to RECIST v1.1. CR: disappearance of all target lesions. PR: At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR. OR=CR+PR China ITT population with measurable disease at baseline consisted of all randomized participants in the China population, whether or not the participant had received the assigned study treatment, and had measurable disease at baseline.

End point type	Secondary
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End point timeframe:

Randomization up to CCOD of 29Aug2019 (up to approximately 18 months)

Notes:

[26] - 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: This endpoint only reports the data for the China population.

End point values	Sorafenib - China	Atezolizumab + Bevacizumab - China		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	130		
Units: percentage of participants				
number (confidence interval 95%)	6.7 (1.85 to 16.20)	24.6 (17.49 to 32.94)		

Statistical analyses

Statistical analysis title	ORR-IRF RECIST v1,1 - China
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Statistical analysis description:

Stratified by macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline AFP (<400 vs. ≥ 400 ng/mL).

Comparison groups	Sorafenib - China v Atezolizumab + Bevacizumab - China
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Number of subjects included in analysis	190
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0036
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	4.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.53
upper limit	13.86

Secondary: Objective Response Rate by IRF-Assessment (ORR-IRF) per Hepatocellular Carcinoma (HCC) modified RECIST (mRECIST) in the China Population

End point title	Objective Response Rate by IRF-Assessment (ORR-IRF) per Hepatocellular Carcinoma (HCC) modified RECIST (mRECIST) in the China Population ^[27]
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End point description:

ORR was defined as the percentage of participants with CR or PR as determined by the IRF according to HCC mRECIST. HCC mRECIST differentiates between vital tumor and necrotic areas in the liver measuring only the residual vital tumor mass in the liver. CR: disappearance of all target lesions. PR: At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR. OR=CR+PR China ITT population with measurable disease at baseline consisted of all randomized participants in the China population, whether or not the participant had received the assigned study treatment, and had measurable disease at baseline.

End point type	Secondary
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End point timeframe:

Randomization up to CCOD of 29Aug2019 (up to approximately 18 months)

Notes:

[27] - 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: This endpoint only reports the data for the China population.

End point values	Sorafenib - China	Atezolizumab + Bevacizumab - China		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	128		
Units: percentage of participants				
number (confidence interval 95%)	8.5 (2.81 to 18.68)	29.7 (21.94 to 38.40)		

Statistical analyses

Statistical analysis title	ORR-IRF HCC mRECIST - China
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Statistical analysis description:

Stratified by macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline AFP (<400 vs. ≥ 400 ng/mL).

Comparison groups	Sorafenib - China v Atezolizumab + Bevacizumab - China
Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0013
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	4.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.72
upper limit	12.87

Secondary: ORR by Investigator-Assessment (ORR-INV) per RECIST v1.1 in the China Population

End point title	ORR by Investigator-Assessment (ORR-INV) per RECIST v1.1 in the China Population ^[28]
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End point description:

ORR was defined as the percentage of participants with CR or PR as determined by the investigator according to RECIST v1.1. CR: disappearance of all target lesions. PR: At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR. OR=CR+PR China ITT population with measurable disease at baseline consisted of all randomized participants in the China population, whether or not the participant had received the assigned study treatment, and had measurable disease at baseline.

End point type	Secondary
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End point timeframe:

Randomization up to CCOD of 29Aug2019 (up to approximately 18 months)

Notes:

[28] - 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: This endpoint only reports the data for the China population.

End point values	Sorafenib - China	Atezolizumab + Bevacizumab - China		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	133		
Units: percentage of participants				
number (confidence interval 95%)	4.9 (1.03 to 13.71)	21.1 (14.47 to 28.97)		

Statistical analyses

Statistical analysis title	ORR-INV RECIST v1.1 - China
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Statistical analysis description:

Stratified by macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline AFP (<400 vs. ≥ 400 ng/mL).

Comparison groups	Sorafenib - China v Atezolizumab + Bevacizumab - China
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Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0052
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	5.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.47
upper limit	17.39

Secondary: Duration of Response by IRF-Assessment (DOR-IRF) per RECIST v1.1 in the China Population

End point title	Duration of Response by IRF-Assessment (DOR-IRF) per RECIST v1.1 in the China Population ^[29]
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End point description:

DOR was defined as the time interval from the date of first occurrence of a documented objective response (CR or PR, whichever status is recorded first) until the first date that disease progression (PD) or death was documented, whichever occurs first as determined by the IRF according to RECIST v1.1. CR: disappearance of all target lesions. PR: At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR. PD: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters on study (including baseline). In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 mm. The analysis population included China participants with a confirmed response (CR or PR). 9999/99999 = not estimable due to the limited number of events observed

End point type	Secondary
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End point timeframe:

Randomization up to CCOD of 29Aug2019 (up to approximately 18 months)

Notes:

[29] - 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: This endpoint only reports the data for the China population.

End point values	Sorafenib - China	Atezolizumab + Bevacizumab - China		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	32		
Units: months				
median (confidence interval 95%)	9999 (4.86 to 99999)	9999 (8.15 to 99999)		

Statistical analyses

Statistical analysis title	DOR-IRF RECIST v1.1 - China
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Statistical analysis description:

Stratified by macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline

AFP (<400 vs. ≥ 400 ng/mL).

Comparison groups	Sorafenib - China v Atezolizumab + Bevacizumab - China
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4581
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	5.85

Secondary: Duration of Response by IRF Assessment (DOR-IRF) per HCC mRECIST in the China Population

End point title	Duration of Response by IRF Assessment (DOR-IRF) per HCC mRECIST in the China Population ^[30]
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End point description:

DOR: the time interval from the date of first occurrence of a documented objective response (CR or PR, whichever status is recorded first) until the first date that disease progression (PD) or death was documented, whichever occurs first as determined by the IRF according to HCC mRECIST. HCC mRECIST differentiates between vital tumor and necrotic areas in the liver, measuring only the residual vital tumor mass in the liver CR: disappearance of all target lesions. PR: At least 30% decrease in the sum of diameters of all target lesions compared to baseline, in the absence of CR. PD: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters on study (including baseline). In addition, the sum of diameters must also demonstrate an absolute increase of ≥ 5 mm. The analysis population included Global participants with a confirmed response (CR or PR). 9999/99999 = not estimable due to the limited number of events observed

End point type	Secondary
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End point timeframe:

Randomization up to CCOD of 29Aug2019 (up to approximately 18 months)

Notes:

[30] - 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: This endpoint only reports the data for the China population.

End point values	Sorafenib - China	Atezolizumab + Bevacizumab - China		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	38		
Units: months				
median (confidence interval 95%)	4.86 (4.47 to 99999)	9999 (8.15 to 99999)		

Statistical analyses

Statistical analysis title	DOR-IRF HCC mRECIST - China
Statistical analysis description: Stratified by macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline AFP (<400 vs. >= 400 ng/mL).	
Comparison groups	Sorafenib - China v Atezolizumab + Bevacizumab - China
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.01
upper limit	0.91

Secondary: Duration of Response by Investigator Assessment (DOR-INV) per RECIST v1.1 in the China Population

End point title	Duration of Response by Investigator Assessment (DOR-INV) per RECIST v1.1 in the China Population ^[31]
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End point description:

DOR was defined as the time interval from the date of first occurrence of a documented objective response (CR or PR, whichever status is recorded first) until the first date that disease progression (PD) or death was documented, whichever occurs first as determined by the investigator according to RECIST v1.1. CR: disappearance of all target lesions. PR: At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR. PD: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters on study (including baseline). In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of >= 5 mm. The analysis population included China participants with a confirmed response (CR or PR). 9999/99999 = not estimable due to the limited number of events observed

End point type	Secondary
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End point timeframe:

Randomization up to CCOD of 29Aug2019 (up to approximately 18 months)

Notes:

[31] - 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: This endpoint only reports the data for the China population.

End point values	Sorafenib - China	Atezolizumab + Bevacizumab - China		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	28		
Units: months				
median (confidence interval 95%)	5.55 (4.17 to 99999)	9999 (9999 to 99999)		

Statistical analyses

Statistical analysis title	DOR-INV RECIST v1.1 - China
Statistical analysis description:	
Stratified by macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline AFP (<400 vs. ≥ 400 ng/mL).	
Comparison groups	Sorafenib - China v Atezolizumab + Bevacizumab - China
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3477
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.03
upper limit	3.69

Secondary: PFS-IRF per HCC mRECIST in the China Population

End point title	PFS-IRF per HCC mRECIST in the China Population ^[32]
End point description:	
PFS was defined as the time from randomization to the first occurrence of progressive disease or death from any cause whichever occurs first as determined by the IRF according to HCC mRECIST. HCC mRECIST differentiates between vital tumor and necrotic areas in the liver, measuring only the residual vital tumor mass in the liver. PD: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters on study (including baseline). In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 millimeters (mm). China ITT population consisted of all randomized participants in the China population, whether or not the participant had received the assigned study treatment.	
End point type	Secondary

End point timeframe:

Randomization to the first occurrence of disease progression or death from any cause up to CCOD of 29Aug2019 (up to approximately 18 months)

Notes:

[32] - 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: This endpoint only reports the data for the China population.

End point values	Sorafenib - China	Atezolizumab + Bevacizumab - China		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	133		
Units: months				
median (confidence interval 95%)	3.19 (2.56 to 4.76)	5.72 (4.17 to 8.11)		

Statistical analyses

Statistical analysis title	PFS-IRF HCC mRECIST - China
Statistical analysis description:	
Stratified by macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline AFP (<400 vs. \geq 400 ng/mL).	
Comparison groups	Sorafenib - China v Atezolizumab + Bevacizumab - China
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0103
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	0.89

Secondary: PFS by Investigator Assessment (PFS-INV) per RECIST v1.1 in the China Population

End point title	PFS by Investigator Assessment (PFS-INV) per RECIST v1.1 in the China Population ^[33]
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End point description:

PFS was defined as the time from randomization to the first occurrence of progressive disease or death from any cause whichever occurs first as determined by the investigator according to RECIST v1.1. PD: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters on study (including baseline). In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of \geq 5 millimeters (mm). China ITT population consisted of all randomized participants in the China population, whether or not the participant had received the assigned study treatment.

End point type	Secondary
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End point timeframe:

Randomization to the first occurrence of disease progression or death from any cause up to CCOD of 29Aug2019 (up to approximately 18 months)

Notes:

[33] - 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: This endpoint only reports the data for the China population.

End point values	Sorafenib - China	Atezolizumab + Bevacizumab - China		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	133		
Units: months				
median (confidence interval 95%)	2.83 (2.73 to 3.98)	5.55 (4.21 to 8.34)		

Statistical analyses

Statistical analysis title	PFS-INV RECIST v1.1 - China
Statistical analysis description: Stratified by macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline AFP (<400 vs. \geq 400 ng/mL).	
Comparison groups	Sorafenib - China v Atezolizumab + Bevacizumab - China
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.33
upper limit	0.71

Secondary: Time to Progression (TTP) by IRF Assessment (TTP-IRF) per RECIST v1.1 in the China Population

End point title	Time to Progression (TTP) by IRF Assessment (TTP-IRF) per RECIST v1.1 in the China Population ^[34]
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End point description:

Time to progression was defined as the time from the date of randomization to the date of the first documented tumor progression as determined by the IRF according to RECIST v1.1. PD: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters on study (including baseline). In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of \geq 5 millimeters (mm). China ITT population consisted of all randomized participants in the China population, whether or not the participant had received the assigned study treatment.

End point type	Secondary
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End point timeframe:

Randomization to the first occurrence of disease progression or death from any cause up to CCOD of 29Aug2019 (up to approximately 18 months)

Notes:

[34] - 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: This endpoint only reports the data for the China population.

End point values	Sorafenib - China	Atezolizumab + Bevacizumab - China		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	133		
Units: months				
median (confidence interval 95%)	4.14 (2.76 to 10.15)	7.00 (5.45 to 9.49)		

Statistical analyses

Statistical analysis title	TTP-IRF RECIST v1.1 - China
Statistical analysis description:	
Stratified by macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline AFP (<400 vs. \geq 400 ng/mL).	
Comparison groups	Sorafenib - China v Atezolizumab + Bevacizumab - China
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0927
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	1.07

Secondary: TTP-IRF per HCC mRECIST in the China Population

End point title	TTP-IRF per HCC mRECIST in the China Population ^[35]
End point description:	
Time to progression was defined as the time from the date of randomization to the date of the first documented tumor progression as determined by the IRF according to HCC mRECIST. HCC mRECIST differentiates between vital tumor and necrotic areas in the liver, measuring only the residual vital tumor mass in the liver. PD: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters on study (including baseline). In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of \geq 5 millimeters (mm). China ITT population consisted of all randomized participants in the China population, whether or not the participant had received the assigned study treatment.	
End point type	Secondary

End point timeframe:

Randomization to the first occurrence of disease progression or death from any cause up to CCOD of 29Aug2019 (up to approximately 18 months)

Notes:

[35] - 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: This endpoint only reports the data for the China population.

End point values	Sorafenib - China	Atezolizumab + Bevacizumab - China		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	133		
Units: months				
median (confidence interval 95%)	4.14 (2.76 to 10.15)	7.00 (5.45 to 9.49)		

Statistical analyses

Statistical analysis title	TTP-IRF HCC mRECIST - China
Statistical analysis description: Stratified by macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline AFP (<400 vs. \geq 400 ng/mL).	
Comparison groups	Sorafenib - China v Atezolizumab + Bevacizumab - China
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0861
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	1.06

Secondary: TTP by Investigator Assessment (TTP-INV) per RECIST v1.1 in the China Population

End point title	TTP by Investigator Assessment (TTP-INV) per RECIST v1.1 in the China Population ^[36]
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End point description:

Time to progression was defined as the time from the date of randomization to the date of the first documented tumor progression as determined by the investigator according to RECIST v1.1. PD: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters on study (including baseline). In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of \geq 5 millimeters (mm). China ITT population consisted of all randomized participants in the China population, whether or not the participant had received the assigned study treatment.

End point type	Secondary
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End point timeframe:

Randomization to the first occurrence of disease progression or death from any cause up to CCOD of 29Aug2019 (up to approximately 18 months)

Notes:

[36] - 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: This endpoint only reports the data for the China population.

End point values	Sorafenib - China	Atezolizumab + Bevacizumab - China		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	133		
Units: months				
median (confidence interval 95%)	2.83 (2.79 to 4.17)	6.83 (5.32 to 9.33)		

Statistical analyses

Statistical analysis title	TTP-INV RECIST v1.1 - China
Statistical analysis description:	
Stratified by macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline AFP (<400 vs. ≥ 400 ng/mL).	
Comparison groups	Sorafenib - China v Atezolizumab + Bevacizumab - China
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.33
upper limit	0.74

Secondary: Time to Deterioration (TTD) in the China Population

End point title	Time to Deterioration (TTD) in the China Population ^[37]
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End point description:

TTD was defined as the time from randomization to the first deterioration (decrease from baseline of ≥ 10 points) in the patient-reported health-related global health status/quality of life (GHS /HRQoL), physical function or role function scales of the European Organization for Research and Treatment of Cancer quality-of-life questionnaire for cancer (EORTC) QLQ-C30, maintained for two consecutive assessments, or one assessment followed by death from any cause within 3 weeks. China ITT population consisted of all randomized participants in the China population, whether or not the participant had received the assigned study treatment. 9999/99999 = not estimable due to the limited number of events observed

End point type	Secondary
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End point timeframe:

Randomization to the first occurrence of disease progression or death from any cause up to CCOD of 29Aug2019 (up to approximately 18 months)

Notes:

[37] - 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: This endpoint only reports the data for the China population.

End point values	Sorafenib - China	Atezolizumab + Bevacizumab - China		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	133		
Units: months				
median (confidence interval 95%)				
Physical Functioning	5.62 (2.10 to 99999)	13.14 (9.69 to 99999)		
Role Functioning	9999 (2.14 to 99999)	9999 (7.20 to 99999)		
GHS/QoL	3.58 (1.48 to 9.82)	9.76 (6.24 to 99999)		

Statistical analyses

Statistical analysis title	TTD Physical Functioning - China
Statistical analysis description: Physical Functioning: Stratified by macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline AFP (<400 vs. ≥ 400 ng/mL).	
Comparison groups	Sorafenib - China v Atezolizumab + Bevacizumab - China
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0035
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.26
upper limit	0.78

Statistical analysis title	TTD GHS/QoL - China
Statistical analysis description: GHS/QoL: Stratified by macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline AFP (<400 vs. ≥ 400 ng/mL).	
Comparison groups	Sorafenib - China v Atezolizumab + Bevacizumab - China
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0135
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.32
upper limit	0.88

Statistical analysis title	TTD Role Functioning - China
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Statistical analysis description:

Role Functioning: Stratified by macrovascular invasion and/or extrahepatic spread (presence vs.

absence), and baseline AFP (<400 vs. ≥ 400 ng/mL).

Comparison groups	Sorafenib - China v Atezolizumab + Bevacizumab - China
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2214
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	1.23

Secondary: Percentage of Participants With Adverse Events (AEs) in the China Population

End point title	Percentage of Participants With Adverse Events (AEs) in the China Population ^[38]
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End point description:

An adverse event is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered as adverse events. China safety population included all randomized China participants who received any amount of study drug with participants grouped according to the treatment the participant actually received.

End point type	Secondary
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End point timeframe:

Up to end of study (up to approximately 40 months)

Notes:

[38] - 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: This endpoint will report the data for the China population after study completion.

End point values	Atezolizumab + Bevacizumab - Global	Sorafenib - China		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[39]	0 ^[40]		
Units: percentage of participants				

Notes:

[39] - To be reported at end of study

[40] - To be reported at end of study

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Serum Concentration (Cmax) of Atezolizumab in the China Population

End point title	Maximum Serum Concentration (Cmax) of Atezolizumab in the China Population ^[41]
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End point description:

The pharmacokinetic (PK)-evaluable population was defined as all participants in the China population who received any dose of study treatment and who had at least one post-baseline PK sample available.

End point type	Secondary
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End point timeframe:

Post-dose on Day 1 of Cycle 1

Notes:

[41] - 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: This endpoint only reports the data for the China population treated with atezolizumab.

End point values	Atezolizumab + Bevacizumab - China			
Subject group type	Reporting group			
Number of subjects analysed	85			
Units: mcg/mL				
arithmetic mean (standard deviation)	456 (± 153)			

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Serum Concentration (Cmin) of Atezolizumab in the China Population

End point title	Trough Serum Concentration (Cmin) of Atezolizumab in the China Population ^[42]
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End point description:

The pharmacokinetic (PK)-evaluable population was defined as all participants in the China population who received any dose of study treatment and who had at least one post-baseline PK sample available.

End point type	Secondary
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End point timeframe:

Pre-dose on Day 1 of Cycles 2, 3, 4, 8, 12 and 16

Notes:

[42] - 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: This endpoint only reports the data for the China population treated with atezolizumab.

End point values	Atezolizumab + Bevacizumab - China			
Subject group type	Reporting group			
Number of subjects analysed	132			
Units: mcg/mL				
arithmetic mean (standard deviation)				
Pre-dose Cycle 2, Day 1; n=87	92.6 (± 65.7)			
Pre-dose Cycle 3, Day 1; n=4	105 (± 36.8)			
Pre-dose Cycle 4, Day 1; n=80	143 (± 61.4)			
Pre-dose Cycle 8, Day 1; n=11	177 (± 61.9)			

Pre-dose Cycle 12, Day 1; n=20	201 (± 97.6)			
Pre-dose Cycle 16, Day 1; n=13	208 (± 79.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Anti-Drug Antibodies (ADAs) to Atezolizumab in the China Population

End point title	Percentage of Participants With Anti-Drug Antibodies (ADAs) to Atezolizumab in the China Population ^[43]
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End point description:

The China ADA-evaluable population was defined as all participants in the China population who received any dose of atezolizumab and who had at least one post-baseline ADA assessment.

End point type	Secondary
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End point timeframe:

Up to CCOD of 29Aug2019 (up to approximately 18 months)

Notes:

[43] - 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: This endpoint only reports the data for the China population treated with atezolizumab.

End point values	Atezolizumab + Bevacizumab - China			
Subject group type	Reporting group			
Number of subjects analysed	132			
Units: percentage of participants				
number (not applicable)				
Baseline; n=90	1.1			
Post-baseline; n=89	20.2			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to clinical cut off date (CCOD) of 31 August, 2020 (up to approximately 30 months)

Adverse event reporting additional description:

Safety population: all randomized participants who received any amount of study drug with participants grouped according to the treatment the participant actually received. Reported here are the analyses of the Global and China safety populations.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.0
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Reporting groups

Reporting group title	Sorafenib - Global
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Reporting group description:

Participants in the Global population received sorafenib until unacceptable toxicity or loss of clinical benefit as determined by the investigator.

Reporting group title	Atezolizumab + Bevacizumab - China
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Reporting group description:

Participants in the China population received Atezolizumab + Bevacizumab until unacceptable toxicity or loss of clinical benefit as determined by the investigator.

Reporting group title	Sorafenib - China
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Reporting group description:

Participants in the China population received sorafenib until unacceptable toxicity or loss of clinical benefit as determined by the investigator.

Reporting group title	Atezolizumab + Bevacizumab - Global
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Reporting group description:

Participants in the Global population received Atezolizumab + Bevacizumab until unacceptable toxicity or loss of clinical benefit as determined by the investigator.

Serious adverse events	Sorafenib - Global	Atezolizumab + Bevacizumab - China	Sorafenib - China
Total subjects affected by serious adverse events			
subjects affected / exposed	51 / 156 (32.69%)	47 / 132 (35.61%)	12 / 58 (20.69%)
number of deaths (all causes)	98	61	37
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Chronic myeloid leukaemia			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric cancer			

subjects affected / exposed	1 / 156 (0.64%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasm			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal squamous cell carcinoma			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour haemorrhage			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour rupture			
subjects affected / exposed	0 / 156 (0.00%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bleeding varicose vein			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolism			
subjects affected / exposed	0 / 156 (0.00%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage			

subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 156 (0.00%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 156 (0.64%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Phlebitis			
subjects affected / exposed	1 / 156 (0.64%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	2 / 156 (1.28%)	1 / 132 (0.76%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 1	0 / 1
Fatigue			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	1 / 156 (0.64%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Multiple organ dysfunction syndrome			

subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	2 / 156 (1.28%)	4 / 132 (3.03%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 2	2 / 7	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytokine release syndrome			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 156 (0.00%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			

subjects affected / exposed	2 / 156 (1.28%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	1 / 156 (0.64%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	1 / 156 (0.64%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hiccups			
subjects affected / exposed	1 / 156 (0.64%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 156 (0.64%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 156 (0.00%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			

subjects affected / exposed	2 / 156 (1.28%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary hypertension			
subjects affected / exposed	1 / 156 (0.64%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delirium			
subjects affected / exposed	0 / 156 (0.00%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 156 (0.00%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Amylase increased			

subjects affected / exposed	1 / 156 (0.64%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 156 (0.64%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	2 / 156 (1.28%)	1 / 132 (0.76%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	2 / 2	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical condition abnormal			
subjects affected / exposed	1 / 156 (0.64%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Granulocyte count decreased			
subjects affected / exposed	0 / 156 (0.00%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lipase increased			
subjects affected / exposed	1 / 156 (0.64%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver function test increased			
subjects affected / exposed	1 / 156 (0.64%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	0 / 156 (0.00%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			

Acetabulum fracture			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Compression fracture			
subjects affected / exposed	1 / 156 (0.64%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	1 / 156 (0.64%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	1 / 156 (0.64%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion related reaction			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic fracture			
subjects affected / exposed	1 / 156 (0.64%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			

Hydrocele			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	0 / 156 (0.00%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 156 (0.64%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 156 (0.64%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 156 (0.00%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cerebral haemorrhage			
subjects affected / exposed	1 / 156 (0.64%)	0 / 132 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	0 / 156 (0.00%)	2 / 132 (1.52%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 156 (0.00%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	1 / 156 (0.64%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 156 (0.00%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic encephalopathy			
subjects affected / exposed	3 / 156 (1.92%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic encephalopathy			
subjects affected / exposed	1 / 156 (0.64%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			

subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural hygroma			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VIth nerve disorder			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VIth nerve paralysis			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 156 (1.28%)	3 / 132 (2.27%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	2 / 2	0 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune thrombocytopenia			
subjects affected / exposed	0 / 156 (0.00%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	2 / 156 (1.28%)	1 / 132 (0.76%)	2 / 58 (3.45%)
occurrences causally related to treatment / all	2 / 2	3 / 3	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			

Hypoacusis			
subjects affected / exposed	0 / 156 (0.00%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Blindness unilateral			
subjects affected / exposed	0 / 156 (0.00%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 156 (0.00%)	2 / 132 (1.52%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	2 / 156 (1.28%)	1 / 132 (0.76%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 156 (0.00%)	2 / 132 (1.52%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal fissure			
subjects affected / exposed	1 / 156 (0.64%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	1 / 156 (0.64%)	3 / 132 (2.27%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	1 / 156 (0.64%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Diarrhoea			
subjects affected / exposed	1 / 156 (0.64%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer			
subjects affected / exposed	1 / 156 (0.64%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric mucosal lesion			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer haemorrhage			
subjects affected / exposed	1 / 156 (0.64%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer perforation			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric varices haemorrhage			
subjects affected / exposed	1 / 156 (0.64%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	3 / 156 (1.92%)	2 / 132 (1.52%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	2 / 4	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Gastrointestinal necrosis			

subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoperitoneum			
subjects affected / exposed	2 / 156 (1.28%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hiatus hernia			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune-mediated enterocolitis			
subjects affected / exposed	0 / 156 (0.00%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incarcerated umbilical hernia			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal haemorrhage			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			

subjects affected / exposed	0 / 156 (0.00%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mesenteric vein thrombosis			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mouth haemorrhage			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal haemorrhage			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal stenosis			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal varices haemorrhage			
subjects affected / exposed	1 / 156 (0.64%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	2 / 156 (1.28%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	1 / 156 (0.64%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			

subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	2 / 156 (1.28%)	5 / 132 (3.79%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	1 / 2	5 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Varices oesophageal			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 156 (0.00%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune hepatitis			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bile duct stone			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			
subjects affected / exposed	1 / 156 (0.64%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			

subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug-induced liver injury			
subjects affected / exposed	1 / 156 (0.64%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic cirrhosis			
subjects affected / exposed	2 / 156 (1.28%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 2	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	2 / 156 (1.28%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic function abnormal			
subjects affected / exposed	1 / 156 (0.64%)	5 / 132 (3.79%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	5 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic pain			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disease			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatorenal failure			

subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatorenal syndrome			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperbilirubinaemia			
subjects affected / exposed	1 / 156 (0.64%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertransaminaemia			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver injury			
subjects affected / exposed	1 / 156 (0.64%)	0 / 132 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Drug eruption			
subjects affected / exposed	1 / 156 (0.64%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersensitivity vasculitis			
subjects affected / exposed	0 / 156 (0.00%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin ulcer			

subjects affected / exposed	1 / 156 (0.64%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxic skin eruption			
subjects affected / exposed	1 / 156 (0.64%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 156 (1.28%)	1 / 132 (0.76%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephritis			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	1 / 156 (0.64%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal haematoma			
subjects affected / exposed	1 / 156 (0.64%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Addison's disease			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophysitis			

subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 156 (0.64%)	0 / 132 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune arthritis			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	0 / 156 (0.00%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Groin pain			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	0 / 156 (0.00%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myositis			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pathological fracture			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendonitis			

subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess limb			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary tract infection			
subjects affected / exposed	0 / 156 (0.00%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Burkholderia pseudomallei infection			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 156 (0.64%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Empyema			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia sepsis			

subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 156 (0.00%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemophilus infection			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis E			
subjects affected / exposed	1 / 156 (0.64%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Herpes simplex encephalitis			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritoneal abscess			
subjects affected / exposed	0 / 156 (0.00%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonsillar abscess			

subjects affected / exposed	1 / 156 (0.64%)	0 / 132 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 156 (0.64%)	3 / 132 (2.27%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Post procedural infection			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 156 (0.00%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 156 (0.00%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Skin infection			
subjects affected / exposed	0 / 156 (0.00%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth infection			
subjects affected / exposed	0 / 156 (0.00%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tuberculosis			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			

subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 156 (0.00%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperammonaemia			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	1 / 156 (0.64%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemic hyperosmolar nonketotic syndrome			

subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	0 / 156 (0.00%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoalbuminaemia			
subjects affected / exposed	1 / 156 (0.64%)	0 / 132 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	1 / 156 (0.64%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	2 / 156 (1.28%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoproteinaemia			
subjects affected / exposed	0 / 156 (0.00%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lactic acidosis			
subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic acidosis			

subjects affected / exposed	0 / 156 (0.00%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 156 (0.00%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Atezolizumab + Bevacizumab - Global		
Total subjects affected by serious adverse events			
subjects affected / exposed	160 / 329 (48.63%)		
number of deaths (all causes)	177		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Chronic myeloid leukaemia			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric cancer			
subjects affected / exposed	0 / 329 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neoplasm			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oesophageal squamous cell carcinoma			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tumour haemorrhage			

subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Tumour rupture			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	2 / 329 (0.61%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Bleeding varicose vein			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Embolism			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Haemorrhage			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	2 / 329 (0.61%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Phlebitis			

subjects affected / exposed	0 / 329 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombosis			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Fatigue			
subjects affected / exposed	2 / 329 (0.61%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	0 / 329 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Multiple organ dysfunction syndrome			
subjects affected / exposed	2 / 329 (0.61%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Pyrexia			
subjects affected / exposed	11 / 329 (3.34%)		
occurrences causally related to treatment / all	3 / 15		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Cytokine release syndrome			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	3 / 329 (0.91%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Epistaxis			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemoptysis			
subjects affected / exposed	0 / 329 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hiccups			

subjects affected / exposed	0 / 329 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	3 / 329 (0.91%)		
occurrences causally related to treatment / all	4 / 5		
deaths causally related to treatment / all	0 / 0		
Pneumonia aspiration			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonitis			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumothorax			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	3 / 329 (0.91%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Pulmonary haemorrhage			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary hypertension			
subjects affected / exposed	0 / 329 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory distress			

subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	2 / 329 (0.61%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Delirium			
subjects affected / exposed	2 / 329 (0.61%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Mental status changes			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Amylase increased			
subjects affected / exposed	0 / 329 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 329 (1.22%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 0		
Blood bilirubin increased			
subjects affected / exposed	5 / 329 (1.52%)		
occurrences causally related to treatment / all	1 / 5		
deaths causally related to treatment / all	0 / 0		

General physical condition abnormal subjects affected / exposed	0 / 329 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Granulocyte count decreased subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lipase increased subjects affected / exposed	0 / 329 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Liver function test increased subjects affected / exposed	0 / 329 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Platelet count decreased subjects affected / exposed	2 / 329 (0.61%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Acetabulum fracture subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Compression fracture subjects affected / exposed	0 / 329 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fall subjects affected / exposed	0 / 329 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Hip fracture			
subjects affected / exposed	2 / 329 (0.61%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Humerus fracture			
subjects affected / exposed	0 / 329 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infusion related reaction			
subjects affected / exposed	4 / 329 (1.22%)		
occurrences causally related to treatment / all	6 / 6		
deaths causally related to treatment / all	0 / 0		
Pelvic fracture			
subjects affected / exposed	0 / 329 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Spinal compression fracture			
subjects affected / exposed	2 / 329 (0.61%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Hydrocele			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute myocardial infarction			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Atrial fibrillation			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiac failure			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	3 / 329 (0.91%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebral haemorrhage			
subjects affected / exposed	0 / 329 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebral infarction			
subjects affected / exposed	2 / 329 (0.61%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular accident			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Encephalopathy			

subjects affected / exposed	1 / 329 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Epilepsy				
subjects affected / exposed	1 / 329 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemorrhage intracranial				
subjects affected / exposed	1 / 329 (0.30%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic encephalopathy				
subjects affected / exposed	4 / 329 (1.22%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Metabolic encephalopathy				
subjects affected / exposed	0 / 329 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subarachnoid haemorrhage				
subjects affected / exposed	1 / 329 (0.30%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Subdural hygroma				
subjects affected / exposed	1 / 329 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	1 / 329 (0.30%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
VIth nerve disorder				

subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
VIth nerve paralysis			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 329 (1.52%)		
occurrences causally related to treatment / all	1 / 7		
deaths causally related to treatment / all	0 / 0		
Immune thrombocytopenia			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	2 / 329 (0.61%)		
occurrences causally related to treatment / all	3 / 4		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Blindness unilateral			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal distension			

subjects affected / exposed	2 / 329 (0.61%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	2 / 329 (0.61%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Abdominal pain upper			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Anal fissure			
subjects affected / exposed	0 / 329 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ascites			
subjects affected / exposed	9 / 329 (2.74%)		
occurrences causally related to treatment / all	1 / 13		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed	4 / 329 (1.22%)		
occurrences causally related to treatment / all	3 / 4		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	5 / 329 (1.52%)		
occurrences causally related to treatment / all	3 / 5		
deaths causally related to treatment / all	0 / 0		
Duodenal ulcer			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Dysphagia			

subjects affected / exposed	2 / 329 (0.61%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastric mucosal lesion			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 329 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastric ulcer perforation			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Gastric varices haemorrhage			
subjects affected / exposed	3 / 329 (0.91%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal haemorrhage			
subjects affected / exposed	10 / 329 (3.04%)		
occurrences causally related to treatment / all	3 / 10		
deaths causally related to treatment / all	1 / 3		
Gastrointestinal necrosis			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematemesis			
subjects affected / exposed	2 / 329 (0.61%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Haemoperitoneum			

subjects affected / exposed	0 / 329 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hiatus hernia				
subjects affected / exposed	1 / 329 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	1 / 329 (0.30%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Immune-mediated enterocolitis				
subjects affected / exposed	1 / 329 (0.30%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Incarcerated umbilical hernia				
subjects affected / exposed	1 / 329 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Large intestinal haemorrhage				
subjects affected / exposed	1 / 329 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Melaena				
subjects affected / exposed	1 / 329 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mesenteric vein thrombosis				
subjects affected / exposed	1 / 329 (0.30%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Mouth haemorrhage				

subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oesophageal haemorrhage			
subjects affected / exposed	3 / 329 (0.91%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Oesophageal stenosis			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oesophageal varices haemorrhage			
subjects affected / exposed	9 / 329 (2.74%)		
occurrences causally related to treatment / all	2 / 10		
deaths causally related to treatment / all	0 / 2		
Pancreatitis			
subjects affected / exposed	2 / 329 (0.61%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Rectal haemorrhage			
subjects affected / exposed	3 / 329 (0.91%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Umbilical hernia			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper gastrointestinal haemorrhage			
subjects affected / exposed	5 / 329 (1.52%)		
occurrences causally related to treatment / all	3 / 5		
deaths causally related to treatment / all	0 / 0		
Varices oesophageal			

subjects affected / exposed	3 / 329 (0.91%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	2 / 329 (0.61%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Autoimmune hepatitis			
subjects affected / exposed	2 / 329 (0.61%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Bile duct stone			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholangitis			
subjects affected / exposed	4 / 329 (1.22%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Cholecystitis			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Drug-induced liver injury			
subjects affected / exposed	0 / 329 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatic cirrhosis			

subjects affected / exposed	3 / 329 (0.91%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Hepatic failure				
subjects affected / exposed	3 / 329 (0.91%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Hepatic function abnormal				
subjects affected / exposed	1 / 329 (0.30%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Hepatic pain				
subjects affected / exposed	1 / 329 (0.30%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatitis				
subjects affected / exposed	1 / 329 (0.30%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disease				
subjects affected / exposed	1 / 329 (0.30%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatorenal failure				
subjects affected / exposed	1 / 329 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatorenal syndrome				
subjects affected / exposed	1 / 329 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Hyperbilirubinaemia				

subjects affected / exposed	3 / 329 (0.91%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Hypertransaminasaemia			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Jaundice			
subjects affected / exposed	2 / 329 (0.61%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Liver injury			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Skin and subcutaneous tissue disorders			
Drug eruption			
subjects affected / exposed	0 / 329 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypersensitivity vasculitis			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin ulcer			
subjects affected / exposed	0 / 329 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Toxic skin eruption			
subjects affected / exposed	0 / 329 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	4 / 329 (1.22%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Haematuria			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nephritis			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	0 / 329 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal haematoma			
subjects affected / exposed	0 / 329 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Addison's disease			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypophysitis			
subjects affected / exposed	2 / 329 (0.61%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 329 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Autoimmune arthritis			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	2 / 329 (0.61%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Groin pain			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Muscular weakness			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Myositis			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pathological fracture			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tendonitis			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abscess limb			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Biliary tract infection			

subjects affected / exposed	1 / 329 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	1 / 329 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Burkholderia pseudomallei infection				
subjects affected / exposed	1 / 329 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	1 / 329 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Device related infection				
subjects affected / exposed	1 / 329 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Empyema				
subjects affected / exposed	1 / 329 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Escherichia sepsis				
subjects affected / exposed	1 / 329 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	2 / 329 (0.61%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Haemophilus infection				

subjects affected / exposed	1 / 329 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatitis E				
subjects affected / exposed	0 / 329 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Herpes simplex encephalitis				
subjects affected / exposed	1 / 329 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	1 / 329 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peritoneal abscess				
subjects affected / exposed	1 / 329 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peritonitis				
subjects affected / exposed	1 / 329 (0.30%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Peritonsillar abscess				
subjects affected / exposed	0 / 329 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	5 / 329 (1.52%)			
occurrences causally related to treatment / all	3 / 5			
deaths causally related to treatment / all	1 / 2			
Post procedural infection				

subjects affected / exposed	1 / 329 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	8 / 329 (2.43%)			
occurrences causally related to treatment / all	1 / 9			
deaths causally related to treatment / all	0 / 1			
Septic shock				
subjects affected / exposed	2 / 329 (0.61%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 1			
Skin infection				
subjects affected / exposed	1 / 329 (0.30%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Tooth infection				
subjects affected / exposed	1 / 329 (0.30%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Tuberculosis				
subjects affected / exposed	1 / 329 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				
subjects affected / exposed	1 / 329 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	3 / 329 (0.91%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Urosepsis				

subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Diabetes mellitus			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperammonaemia			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemic hyperosmolar nonketotic syndrome			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperkalaemia			
subjects affected / exposed	2 / 329 (0.61%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypoalbuminaemia			

subjects affected / exposed	0 / 329 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	2 / 329 (0.61%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoproteinaemia			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lactic acidosis			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolic acidosis			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 329 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Sorafenib - Global	Atezolizumab + Bevacizumab - China	Sorafenib - China
Total subjects affected by non-serious adverse events			
subjects affected / exposed	147 / 156 (94.23%)	129 / 132 (97.73%)	55 / 58 (94.83%)
Vascular disorders			
Hypertension			
subjects affected / exposed	38 / 156 (24.36%)	51 / 132 (38.64%)	12 / 58 (20.69%)
occurrences (all)	43	80	15
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	21 / 156 (13.46%)	10 / 132 (7.58%)	3 / 58 (5.17%)
occurrences (all)	22	11	3
Fatigue			
subjects affected / exposed	29 / 156 (18.59%)	17 / 132 (12.88%)	6 / 58 (10.34%)
occurrences (all)	31	22	6
Oedema peripheral			
subjects affected / exposed	6 / 156 (3.85%)	9 / 132 (6.82%)	3 / 58 (5.17%)
occurrences (all)	6	12	3
Pyrexia			
subjects affected / exposed	15 / 156 (9.62%)	22 / 132 (16.67%)	6 / 58 (10.34%)
occurrences (all)	22	30	9
Malaise			
subjects affected / exposed	5 / 156 (3.21%)	5 / 132 (3.79%)	3 / 58 (5.17%)
occurrences (all)	5	5	3
Pain			
subjects affected / exposed	1 / 156 (0.64%)	9 / 132 (6.82%)	1 / 58 (1.72%)
occurrences (all)	1	10	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	15 / 156 (9.62%)	13 / 132 (9.85%)	5 / 58 (8.62%)
occurrences (all)	18	16	6
Dyspnoea			
subjects affected / exposed	5 / 156 (3.21%)	5 / 132 (3.79%)	2 / 58 (3.45%)
occurrences (all)	5	5	2

Dysphonia subjects affected / exposed occurrences (all)	11 / 156 (7.05%) 11	6 / 132 (4.55%) 6	3 / 58 (5.17%) 3
Epistaxis subjects affected / exposed occurrences (all)	6 / 156 (3.85%) 6	10 / 132 (7.58%) 10	2 / 58 (3.45%) 2
Haemoptysis subjects affected / exposed occurrences (all)	4 / 156 (2.56%) 4	1 / 132 (0.76%) 1	3 / 58 (5.17%) 3
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	11 / 156 (7.05%) 11	9 / 132 (6.82%) 10	5 / 58 (8.62%) 5
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	14 / 156 (8.97%) 18	29 / 132 (21.97%) 48	12 / 58 (20.69%) 18
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	27 / 156 (17.31%) 30	39 / 132 (29.55%) 73	19 / 58 (32.76%) 23
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	11 / 156 (7.05%) 12	19 / 132 (14.39%) 26	7 / 58 (12.07%) 9
Blood bilirubin increased subjects affected / exposed occurrences (all)	23 / 156 (14.74%) 27	31 / 132 (23.48%) 71	14 / 58 (24.14%) 16
Blood creatinine increased subjects affected / exposed occurrences (all)	1 / 156 (0.64%) 1	9 / 132 (6.82%) 16	0 / 58 (0.00%) 0
Platelet count decreased subjects affected / exposed occurrences (all)	18 / 156 (11.54%) 22	27 / 132 (20.45%) 46	10 / 58 (17.24%) 11
Weight decreased subjects affected / exposed occurrences (all)	15 / 156 (9.62%) 18	18 / 132 (13.64%) 19	6 / 58 (10.34%) 9
White blood cell count decreased			

subjects affected / exposed	9 / 156 (5.77%)	20 / 132 (15.15%)	9 / 58 (15.52%)
occurrences (all)	20	61	14
Bilirubin conjugated increased			
subjects affected / exposed	4 / 156 (2.56%)	12 / 132 (9.09%)	6 / 58 (10.34%)
occurrences (all)	7	24	10
Blood bilirubin unconjugated increased			
subjects affected / exposed	1 / 156 (0.64%)	7 / 132 (5.30%)	2 / 58 (3.45%)
occurrences (all)	1	16	2
Blood lactate dehydrogenase increased			
subjects affected / exposed	7 / 156 (4.49%)	10 / 132 (7.58%)	9 / 58 (15.52%)
occurrences (all)	10	12	13
Gamma-glutamyltransferase increased			
subjects affected / exposed	7 / 156 (4.49%)	15 / 132 (11.36%)	9 / 58 (15.52%)
occurrences (all)	7	16	9
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 156 (0.00%)	11 / 132 (8.33%)	0 / 58 (0.00%)
occurrences (all)	0	13	0
Neutrophil count decreased			
subjects affected / exposed	5 / 156 (3.21%)	16 / 132 (12.12%)	5 / 58 (8.62%)
occurrences (all)	11	43	6
Lymphocyte count decreased			
subjects affected / exposed	2 / 156 (1.28%)	8 / 132 (6.06%)	3 / 58 (5.17%)
occurrences (all)	4	12	5
Protein urine present			
subjects affected / exposed	4 / 156 (2.56%)	4 / 132 (3.03%)	5 / 58 (8.62%)
occurrences (all)	4	8	5
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	0 / 156 (0.00%)	13 / 132 (9.85%)	0 / 58 (0.00%)
occurrences (all)	0	13	0
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 156 (7.05%)	12 / 132 (9.09%)	2 / 58 (3.45%)
occurrences (all)	13	16	4

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	14 / 156 (8.97%)	25 / 132 (18.94%)	8 / 58 (13.79%)
occurrences (all)	15	38	9
Leukopenia			
subjects affected / exposed	4 / 156 (2.56%)	18 / 132 (13.64%)	4 / 58 (6.90%)
occurrences (all)	6	30	6
Neutropenia			
subjects affected / exposed	4 / 156 (2.56%)	11 / 132 (8.33%)	3 / 58 (5.17%)
occurrences (all)	7	19	6
Thrombocytopenia			
subjects affected / exposed	7 / 156 (4.49%)	22 / 132 (16.67%)	5 / 58 (8.62%)
occurrences (all)	8	41	5
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	5 / 156 (3.21%)	14 / 132 (10.61%)	4 / 58 (6.90%)
occurrences (all)	5	14	4
Abdominal pain			
subjects affected / exposed	27 / 156 (17.31%)	18 / 132 (13.64%)	10 / 58 (17.24%)
occurrences (all)	31	22	15
Abdominal pain upper			
subjects affected / exposed	9 / 156 (5.77%)	5 / 132 (3.79%)	4 / 58 (6.90%)
occurrences (all)	9	6	4
Ascites			
subjects affected / exposed	8 / 156 (5.13%)	7 / 132 (5.30%)	2 / 58 (3.45%)
occurrences (all)	10	8	3
Constipation			
subjects affected / exposed	25 / 156 (16.03%)	17 / 132 (12.88%)	5 / 58 (8.62%)
occurrences (all)	27	19	5
Diarrhoea			
subjects affected / exposed	78 / 156 (50.00%)	16 / 132 (12.12%)	26 / 58 (44.83%)
occurrences (all)	105	22	36
Nausea			
subjects affected / exposed	25 / 156 (16.03%)	17 / 132 (12.88%)	7 / 58 (12.07%)
occurrences (all)	28	21	9
Stomatitis			

subjects affected / exposed occurrences (all)	7 / 156 (4.49%) 7	3 / 132 (2.27%) 3	2 / 58 (3.45%) 2
Vomiting subjects affected / exposed occurrences (all)	14 / 156 (8.97%) 14	15 / 132 (11.36%) 25	5 / 58 (8.62%) 5
Gingival bleeding subjects affected / exposed occurrences (all)	0 / 156 (0.00%) 0	9 / 132 (6.82%) 12	1 / 58 (1.72%) 1
Hepatobiliary disorders Hepatic function abnormal subjects affected / exposed occurrences (all)	4 / 156 (2.56%) 4	7 / 132 (5.30%) 8	3 / 58 (5.17%) 3
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	22 / 156 (14.10%) 22	2 / 132 (1.52%) 2	7 / 58 (12.07%) 7
Palmar-plantar erythrodysaesthesia syndrome subjects affected / exposed occurrences (all)	75 / 156 (48.08%) 81	2 / 132 (1.52%) 2	33 / 58 (56.90%) 39
Pruritus subjects affected / exposed occurrences (all)	15 / 156 (9.62%) 16	23 / 132 (17.42%) 27	7 / 58 (12.07%) 8
Rash subjects affected / exposed occurrences (all)	28 / 156 (17.95%) 28	18 / 132 (13.64%) 20	7 / 58 (12.07%) 7
Rash maculo-papular subjects affected / exposed occurrences (all)	5 / 156 (3.21%) 6	3 / 132 (2.27%) 3	3 / 58 (5.17%) 4
Renal and urinary disorders Proteinuria subjects affected / exposed occurrences (all)	13 / 156 (8.33%) 19	66 / 132 (50.00%) 114	11 / 58 (18.97%) 18
Haematuria subjects affected / exposed occurrences (all)	0 / 156 (0.00%) 0	8 / 132 (6.06%) 14	0 / 58 (0.00%) 0
Cylindruria			

subjects affected / exposed occurrences (all)	0 / 156 (0.00%) 0	8 / 132 (6.06%) 20	0 / 58 (0.00%) 0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	3 / 156 (1.92%)	16 / 132 (12.12%)	1 / 58 (1.72%)
occurrences (all)	3	19	1
Hyperthyroidism			
subjects affected / exposed	0 / 156 (0.00%)	9 / 132 (6.82%)	0 / 58 (0.00%)
occurrences (all)	0	11	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 156 (4.49%)	5 / 132 (3.79%)	0 / 58 (0.00%)
occurrences (all)	8	7	0
Back pain			
subjects affected / exposed	6 / 156 (3.85%)	9 / 132 (6.82%)	5 / 58 (8.62%)
occurrences (all)	6	9	7
Musculoskeletal pain			
subjects affected / exposed	3 / 156 (1.92%)	9 / 132 (6.82%)	1 / 58 (1.72%)
occurrences (all)	3	9	1
Myalgia			
subjects affected / exposed	5 / 156 (3.21%)	4 / 132 (3.03%)	2 / 58 (3.45%)
occurrences (all)	6	4	2
Pain in extremity			
subjects affected / exposed	6 / 156 (3.85%)	2 / 132 (1.52%)	3 / 58 (5.17%)
occurrences (all)	6	2	3
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 156 (2.56%)	7 / 132 (5.30%)	1 / 58 (1.72%)
occurrences (all)	4	10	1
Upper respiratory tract infection			
subjects affected / exposed	2 / 156 (1.28%)	20 / 132 (15.15%)	2 / 58 (3.45%)
occurrences (all)	2	24	2
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	39 / 156 (25.00%)	24 / 132 (18.18%)	12 / 58 (20.69%)
occurrences (all)	50	26	15

Hyperglycaemia subjects affected / exposed occurrences (all)	4 / 156 (2.56%) 5	13 / 132 (9.85%) 26	0 / 58 (0.00%) 0
Hypoalbuminaemia subjects affected / exposed occurrences (all)	11 / 156 (7.05%) 13	28 / 132 (21.21%) 36	5 / 58 (8.62%) 8
Hypokalaemia subjects affected / exposed occurrences (all)	11 / 156 (7.05%) 13	11 / 132 (8.33%) 16	11 / 58 (18.97%) 12
Hyponatraemia subjects affected / exposed occurrences (all)	7 / 156 (4.49%) 7	7 / 132 (5.30%) 11	4 / 58 (6.90%) 4
Hypophosphataemia subjects affected / exposed occurrences (all)	11 / 156 (7.05%) 13	3 / 132 (2.27%) 5	6 / 58 (10.34%) 10
Hypoproteinaemia subjects affected / exposed occurrences (all)	1 / 156 (0.64%) 1	7 / 132 (5.30%) 9	1 / 58 (1.72%) 1

Non-serious adverse events	Atezolizumab + Bevacizumab - Global		
Total subjects affected by non-serious adverse events subjects affected / exposed	310 / 329 (94.22%)		
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	114 / 329 (34.65%) 180		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all)	25 / 329 (7.60%) 29		
Fatigue subjects affected / exposed occurrences (all)	73 / 329 (22.19%) 88		
Oedema peripheral subjects affected / exposed occurrences (all)	35 / 329 (10.64%) 41		

Pyrexia			
subjects affected / exposed	58 / 329 (17.63%)		
occurrences (all)	82		
Malaise			
subjects affected / exposed	13 / 329 (3.95%)		
occurrences (all)	13		
Pain			
subjects affected / exposed	9 / 329 (2.74%)		
occurrences (all)	10		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	46 / 329 (13.98%)		
occurrences (all)	53		
Dyspnoea			
subjects affected / exposed	26 / 329 (7.90%)		
occurrences (all)	27		
Dysphonia			
subjects affected / exposed	31 / 329 (9.42%)		
occurrences (all)	35		
Epistaxis			
subjects affected / exposed	36 / 329 (10.94%)		
occurrences (all)	44		
Haemoptysis			
subjects affected / exposed	4 / 329 (1.22%)		
occurrences (all)	4		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	34 / 329 (10.33%)		
occurrences (all)	36		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	53 / 329 (16.11%)		
occurrences (all)	74		
Aspartate aminotransferase increased			
subjects affected / exposed	73 / 329 (22.19%)		
occurrences (all)	110		

Blood alkaline phosphatase increased			
subjects affected / exposed	31 / 329 (9.42%)		
occurrences (all)	41		
Blood bilirubin increased			
subjects affected / exposed	56 / 329 (17.02%)		
occurrences (all)	99		
Blood creatinine increased			
subjects affected / exposed	17 / 329 (5.17%)		
occurrences (all)	28		
Platelet count decreased			
subjects affected / exposed	45 / 329 (13.68%)		
occurrences (all)	65		
Weight decreased			
subjects affected / exposed	46 / 329 (13.98%)		
occurrences (all)	50		
White blood cell count decreased			
subjects affected / exposed	18 / 329 (5.47%)		
occurrences (all)	54		
Bilirubin conjugated increased			
subjects affected / exposed	11 / 329 (3.34%)		
occurrences (all)	23		
Blood bilirubin unconjugated increased			
subjects affected / exposed	7 / 329 (2.13%)		
occurrences (all)	16		
Blood lactate dehydrogenase increased			
subjects affected / exposed	10 / 329 (3.04%)		
occurrences (all)	12		
Gamma-glutamyltransferase increased			
subjects affected / exposed	10 / 329 (3.04%)		
occurrences (all)	11		
Blood thyroid stimulating hormone increased			
subjects affected / exposed	10 / 329 (3.04%)		
occurrences (all)	13		
Neutrophil count decreased			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Lymphocyte count decreased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Protein urine present</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>14 / 329 (4.26%)</p> <p>33</p> <p>14 / 329 (4.26%)</p> <p>20</p> <p>2 / 329 (0.61%)</p> <p>4</p>		
<p>Injury, poisoning and procedural complications</p> <p>Infusion related reaction</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>33 / 329 (10.03%)</p> <p>39</p>		
<p>Nervous system disorders</p> <p>Headache</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>32 / 329 (9.73%)</p> <p>38</p>		
<p>Blood and lymphatic system disorders</p> <p>Anaemia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Leukopenia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Neutropenia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Thrombocytopenia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>35 / 329 (10.64%)</p> <p>48</p> <p>20 / 329 (6.08%)</p> <p>31</p> <p>18 / 329 (5.47%)</p> <p>26</p> <p>31 / 329 (9.42%)</p> <p>44</p>		
<p>Gastrointestinal disorders</p> <p>Abdominal distension</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Abdominal pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>25 / 329 (7.60%)</p> <p>25</p> <p>46 / 329 (13.98%)</p> <p>56</p>		

Abdominal pain upper subjects affected / exposed occurrences (all)	17 / 329 (5.17%) 24		
Ascites subjects affected / exposed occurrences (all)	28 / 329 (8.51%) 31		
Constipation subjects affected / exposed occurrences (all)	55 / 329 (16.72%) 60		
Diarrhoea subjects affected / exposed occurrences (all)	67 / 329 (20.36%) 98		
Nausea subjects affected / exposed occurrences (all)	48 / 329 (14.59%) 62		
Stomatitis subjects affected / exposed occurrences (all)	19 / 329 (5.78%) 21		
Vomiting subjects affected / exposed occurrences (all)	34 / 329 (10.33%) 49		
Gingival bleeding subjects affected / exposed occurrences (all)	11 / 329 (3.34%) 14		
Hepatobiliary disorders Hepatic function abnormal subjects affected / exposed occurrences (all)	7 / 329 (2.13%) 7		
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	6 / 329 (1.82%) 6		
Palmar-plantar erythrodysaesthesia syndrome subjects affected / exposed occurrences (all)	6 / 329 (1.82%) 7		
Pruritus			

subjects affected / exposed	70 / 329 (21.28%)		
occurrences (all)	92		
Rash			
subjects affected / exposed	45 / 329 (13.68%)		
occurrences (all)	49		
Rash maculo-papular			
subjects affected / exposed	10 / 329 (3.04%)		
occurrences (all)	11		
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	100 / 329 (30.40%)		
occurrences (all)	163		
Haematuria			
subjects affected / exposed	13 / 329 (3.95%)		
occurrences (all)	19		
Cylindruria			
subjects affected / exposed	7 / 329 (2.13%)		
occurrences (all)	19		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	36 / 329 (10.94%)		
occurrences (all)	40		
Hyperthyroidism			
subjects affected / exposed	16 / 329 (4.86%)		
occurrences (all)	17		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	39 / 329 (11.85%)		
occurrences (all)	44		
Back pain			
subjects affected / exposed	24 / 329 (7.29%)		
occurrences (all)	27		
Musculoskeletal pain			
subjects affected / exposed	28 / 329 (8.51%)		
occurrences (all)	29		
Myalgia			

subjects affected / exposed occurrences (all)	20 / 329 (6.08%) 23		
Pain in extremity subjects affected / exposed occurrences (all)	9 / 329 (2.74%) 9		
Infections and infestations			
Nasopharyngitis subjects affected / exposed occurrences (all)	21 / 329 (6.38%) 27		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	23 / 329 (6.99%) 26		
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	65 / 329 (19.76%) 72		
Hyperglycaemia subjects affected / exposed occurrences (all)	21 / 329 (6.38%) 34		
Hypoalbuminaemia subjects affected / exposed occurrences (all)	37 / 329 (11.25%) 44		
Hypokalaemia subjects affected / exposed occurrences (all)	11 / 329 (3.34%) 14		
Hyponatraemia subjects affected / exposed occurrences (all)	25 / 329 (7.60%) 31		
Hypophosphataemia subjects affected / exposed occurrences (all)	9 / 329 (2.74%) 10		
Hypoproteinaemia subjects affected / exposed occurrences (all)	3 / 329 (0.91%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 March 2018	<p>Given that sorafenib has been shown to prolong the QT and QTc interval, which could lead to an increased risk of ventricular arrhythmia, two exclusion criteria were added to exclude subjects with a history of congenital long QT syndrome or corrected QT interval >500 ms (calculated through the use of the Fridericia method) at screening and subjects with a history of uncorrectable electrolyte disorder affecting serum levels of potassium, calcium, or magnesium. Under the same rationale, it was specified that caution is recommended when administering sorafenib with certain anti-arrhythmic medicines or other medicinal products that lead to QT prolongation in sorafenib-treated participants. The stratification factors to be used for stratified analyses planned to be conducted for both co-primary efficacy endpoints, overall survival (OS) and overall response rate (ORR), were clarified. The following stratification factors were to be used for the stratified analyses that were planned to be conducted for both co-primary endpoints: geographic region (Asia excluding Japan vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline alpha-fetoprotein level (<400 vs. ≥400 ng/mL). Results from unstratified analyses may be provided as sensitivity analyses. Language to describe how the homogeneity of treatment effects across important patient subgroups will be descriptively assessed was added to the statistical details provided for the primary efficacy analyses of OS and ORR. The testing order of the key secondary endpoints was removed as the time to progression was no longer planned to be formally tested. The optional interim analysis was removed.</p>
15 September 2018	<p>The co-primary endpoint of objective response rate (ORR) was changed to progression-free survival (PFS). ORR by investigator assessment was added as a secondary efficacy endpoint. The eligibility criteria were updated to refine the patient population, with the intent to ensure the safety of participants considering the toxicity profile of the study drugs. The window for assessing ECOG performance status, Child-Pugh Class A, and adequate hematologic and end-organ function lab tests was shortened from 14 days to 7 days prior to randomization to ensure fit participants were enrolled and to exclude subjects who could have progressively deteriorating liver function and overall health status. To ensure the safety of participants who would potentially receive bevacizumab (in combination with atezolizumab), the following eligibility criteria were modified/added: 1) Clarified the type of excluded, untreated or incompletely treated varices with bleeding or high risk for bleeding, esophageal and/or gastric varices in the relevant exclusion criteria; 2) The windows for previous stereotactic radiotherapy (within 7 days) and whole brain radiotherapy (within 14 days) were both extended to 28 days prior to initiation of study treatment; 3) A prior bleeding event due to esophageal and/or gastric varices within 6 months prior to initiation of study treatment was added as an exclusion criterion; 4) Local therapy to liver within 28 days prior to initiation of study treatment or non-recovery from side effects of any such procedure was added as an exclusion criterion. The requirement to hold bevacizumab or sorafenib treatment during palliative radiotherapy treatment and the need to obtain Medical Monitor approval prior to continuation of bevacizumab or sorafenib treatment upon completion of such therapy was added. For participants receiving sorafenib, prohibition of strong CYP3A inducers was removed. Additional atezolizumab anti-drug antibody (ADA) and PK samples were added.</p>

20 February 2019	The protocol was amended primarily to modify the statistical analysis plan to include a second interim analysis for overall survival (OS), which should be conducted when approximately 243 OS events (78% information fraction) have been observed. Guidelines for managing participants who experience atezolizumab-associated adverse events were revised to include guidelines for immune-related myositis. The secondary endpoint for patient reported outcomes of time to deterioration (TTD) was amended to align with the co-primary endpoints of progression-free survival and OS. The previous TTD endpoint was added as an exploratory endpoint. Modifications were made to the statistical analysis plan to add progression-free survival as the primary endpoint for the China subpopulation analysis to align with the global study analysis. Anaphylaxis Precautions appendix was modified to remove the requirement for use of a tourniquet. The application of a tourniquet is no longer recommended due to the limited therapeutic benefit and risk of losing time for more important measures. Guidelines for managing participants who experience bevacizumab-associated adverse events were revised to update guidelines on proteinuria.
15 January 2020	The protocol was modified primarily with an update to the risks and management guidelines for atezolizumab to align with the latest atezolizumab Investigator's Brochure.
01 February 2021	The descriptive and optional nature of subsequent overall survival (OS) analyses once statistical significance is reached at any of the pre-planned interim analyses of OS was clarified. Severe Cutaneous Adverse Reactions (SCARs) were added as a risk associated with atezolizumab. The Management Guidelines for Dermatologic Events was updated to include updated management guidelines for Grade 3 dermatologic events and new guidelines for Stevens-Johnson syndrome or toxic epidermal necrolysis of any grade were added. COVID-19 Considerations section was added to describe COVID-19-related risks. Exclusion criteria: Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia was updated to include any active infection that, the opinion of the investigator, could impact patient safety. COVID-19 risk language was included in the Safety Plan, to state that patients with an active infection were to be excluded from study participation. The Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome were updated to include COVID-19 risk language.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported