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	17 November 2022

Results information

Result version number	v2 (current)
This version publication date	21 October 2023
First version publication date	01 September 2021
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	YO40245

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	Final
Date of interim/final analysis	17 November 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 November 2022
Was the trial ended prematurely?	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

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
Consent withdrawn by subject	20	21	8
Physician decision	1	-	-
Study Ended by Sponsor	26	80	5
Death	115	228	46
Lost to follow-up	3	6	2
Reason Unspecified	-	1	-

Number of subjects in period 1	Atezolizumab + Bevacizumab - China

Started	133
Completed	0
Not completed	133
Consent withdrawn by subject	6
Physician decision	-
Study Ended by Sponsor	36
Death	88
Lost to follow-up	3
Reason Unspecified	-

Baseline characteristics

Reporting groups	
Reporting group title	Overall Period

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 is only reporting 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 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

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

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]

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 is only reporting 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 is only reporting 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 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

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

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]

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

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 is only reporting 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

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	= 0.0117
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: 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[5]

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

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 is only reporting 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

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	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: 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]

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

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 is only reporting 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

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	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: 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[7]

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

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 is only reporting 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

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	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: 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[8]

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 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

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 is only reporting 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. >/= 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: 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]

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

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 is only reporting 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

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	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 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[10]

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

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 is only reporting 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

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: PFS-IRF per HCC mRECIST in the Global Population

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

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). 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

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 is only reporting 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]

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

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 is only reporting 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]

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

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 is only reporting 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. >/= 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 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[14]

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 >/= 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

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 is only reporting 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: TTP-IRF per HCC mRECIST in the Global Population

End point title	TTP-IRF per HCC mRECIST in the Global Population[15]

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 >/= 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

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 is only reporting 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. >/= 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: Overall Survival by Baseline AFP in the Global Population

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

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

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 is only reporting 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	= 0.0879
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

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

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 is only reporting 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]

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

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 is only reporting 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

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]

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

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:

[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 is only reporting 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

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]

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

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 is only reporting 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	156	329		
Units: percentage of participants	154	322		

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[21]

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

End point timeframe:

Post-dose on Day 1 of Cycle 1

Notes:

[21] - 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 is only reporting the data for the Global population.

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[22]

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

End point timeframe:

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

Notes:

[22] - 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 is only reporting the data for the Global population.

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[23]

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

End point timeframe:

Baseline and post-baseline on Day 1 (pre-dose) of Cycles 2, 3, 4, 8, 12, 16 (cycle length = 21 days) and treatment discontinuation visit (up to approximately 30 months)

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 is only reporting the data for the Global population.

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[24]

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

End point timeframe:

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

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 is only reporting 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

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	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[25]

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

End point timeframe:

Randomization up to CCOD of 29Aug2019 (up to approximately 18 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 is only reporting 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

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[26]

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

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 is only reporting 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

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	= 0.0052
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[27]

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

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 is only reporting 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

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 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[28]

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

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 is only reporting 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: 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[29]

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

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 is only reporting 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: PFS-IRF per HCC mRECIST in the China Population

End point title	PFS-IRF per HCC mRECIST in the China Population[30]

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:

[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 is only reporting 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. >/= 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[31]

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). 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:

[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 is only reporting 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. >/= 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: TTP-IRF per HCC mRECIST in the China Population

End point title	TTP-IRF per HCC mRECIST in the China Population[32]

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 >/= 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 is only reporting 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. >/= 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: 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[33]

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). 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:

[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 is only reporting 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. >/= 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: Time to Deterioration (TTD) in the China Population

End point title	Time to Deterioration (TTD) in the China Population[34]

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

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 is only reporting 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
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: 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[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 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). 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 is only reporting 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: 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[36]

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

End point timeframe:

Up to end of study (up to approximately 40 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 is only reporting 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	58	132		
Units: percentage of participants	56	131		

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[37]

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

End point timeframe:

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

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 is only reporting the data for the China population.

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

End point title	Maximum Serum Concentration (Cmax) of Atezolizumab in the China Population[38]

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

End point timeframe:

Post-dose on Day 1 of Cycle 1

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 is only reporting the data for the China population.

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: 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[39]

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

End point timeframe:

Baseline and post-baseline on Day 1 (pre-dose) of Cycles 2, 3, 4, 8, 12, 16 (cycle length = 21 days) and treatment discontinuation visit (up to approximately 18 months)

Notes:

[39] - 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 is only reporting the data for the China population.

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:

Up to end of study (up to approximately 56 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

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

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	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.

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	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.

Serious adverse events	Atezolizumab + Bevacizumab - Global	Atezolizumab + Bevacizumab - China	Sorafenib - China
Total subjects affected by serious adverse events			
subjects affected / exposed	171 / 329 (51.98%)	54 / 132 (40.91%)	12 / 58 (20.69%)
number of deaths (all causes)	227	88	45
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Oesophageal squamous cell carcinoma			
subjects affected / exposed	1 / 329 (0.30%)	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	1 / 329 (0.30%)	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
Chronic myeloid leukaemia			
subjects affected / exposed	1 / 329 (0.30%)	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
Gastric cancer			
subjects affected / exposed	0 / 329 (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	1 / 329 (0.30%)	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
Tumour rupture			
subjects affected / exposed	1 / 329 (0.30%)	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
Vascular disorders			
Bleeding varicose vein			
subjects affected / exposed	1 / 329 (0.30%)	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
Deep vein thrombosis			
subjects affected / exposed	2 / 329 (0.61%)	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
Embolism			
subjects affected / exposed	1 / 329 (0.30%)	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
Haemorrhage			

subjects affected / exposed	1 / 329 (0.30%)	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
Hypertension			
subjects affected / exposed	3 / 329 (0.91%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	2 / 3	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			
subjects affected / exposed	1 / 329 (0.30%)	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
Phlebitis			
subjects affected / exposed	0 / 329 (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
Hypotension			
subjects affected / exposed	1 / 329 (0.30%)	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
Peripheral vascular disorder			
subjects affected / exposed	1 / 329 (0.30%)	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
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 329 (0.30%)	1 / 132 (0.76%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 1
Fatigue			
subjects affected / exposed	2 / 329 (0.61%)	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
General physical health deterioration			

subjects affected / exposed	0 / 329 (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
Multiple organ dysfunction syndrome			
subjects affected / exposed	2 / 329 (0.61%)	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 / 2	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	11 / 329 (3.34%)	4 / 132 (3.03%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	3 / 15	2 / 7	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	1 / 329 (0.30%)	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
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 329 (0.30%)	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
Cytokine release syndrome			
subjects affected / exposed	1 / 329 (0.30%)	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
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	1 / 329 (0.30%)	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
Scrotal dermatitis			
subjects affected / exposed	1 / 329 (0.30%)	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

Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 329 (0.30%)	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
Asthma			
subjects affected / exposed	1 / 329 (0.30%)	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
Haemoptysis			
subjects affected / exposed	0 / 329 (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	3 / 329 (0.91%)	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
Epistaxis			
subjects affected / exposed	1 / 329 (0.30%)	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
Pulmonary haemorrhage			
subjects affected / exposed	1 / 329 (0.30%)	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
Pulmonary embolism			
subjects affected / exposed	3 / 329 (0.91%)	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
Pneumothorax			
subjects affected / exposed	1 / 329 (0.30%)	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

Pneumonitis			
subjects affected / exposed	2 / 329 (0.61%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	3 / 329 (0.91%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	4 / 5	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hiccups			
subjects affected / exposed	0 / 329 (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	0 / 329 (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
Respiratory distress			
subjects affected / exposed	1 / 329 (0.30%)	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
Acute pulmonary oedema			
subjects affected / exposed	1 / 329 (0.30%)	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
Cough			
subjects affected / exposed	1 / 329 (0.30%)	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
Orthopnoea			
subjects affected / exposed	1 / 329 (0.30%)	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
Psychiatric disorders			

Mental status changes			
subjects affected / exposed	1 / 329 (0.30%)	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
Delirium			
subjects affected / exposed	2 / 329 (0.61%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	2 / 329 (0.61%)	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
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 329 (0.30%)	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
Amylase increased			
subjects affected / exposed	0 / 329 (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
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 329 (1.22%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	2 / 4	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	7 / 329 (2.13%)	2 / 132 (1.52%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	2 / 7	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical condition abnormal			
subjects affected / exposed	0 / 329 (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

Granulocyte count decreased			
subjects affected / exposed	1 / 329 (0.30%)	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
Lipase increased			
subjects affected / exposed	0 / 329 (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
Platelet count decreased			
subjects affected / exposed	2 / 329 (0.61%)	2 / 132 (1.52%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	1 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver function test increased			
subjects affected / exposed	0 / 329 (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
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 329 (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
Acetabulum fracture			
subjects affected / exposed	1 / 329 (0.30%)	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
Compression fracture			
subjects affected / exposed	0 / 329 (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
Hip fracture			
subjects affected / exposed	2 / 329 (0.61%)	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

Humerus fracture			
subjects affected / exposed	0 / 329 (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
Infusion related reaction			
subjects affected / exposed	4 / 329 (1.22%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	6 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic fracture			
subjects affected / exposed	0 / 329 (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
Spinal compression fracture			
subjects affected / exposed	2 / 329 (0.61%)	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
Subdural haematoma			
subjects affected / exposed	1 / 329 (0.30%)	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
Toxicity to various agents			
subjects affected / exposed	1 / 329 (0.30%)	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
Congenital, familial and genetic disorders			
Hydrocele			
subjects affected / exposed	1 / 329 (0.30%)	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
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 329 (0.30%)	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

Cardiac failure			
subjects affected / exposed	1 / 329 (0.30%)	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
Atrial fibrillation			
subjects affected / exposed	1 / 329 (0.30%)	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
Cardiac arrest			
subjects affected / exposed	1 / 329 (0.30%)	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
Acute myocardial infarction			
subjects affected / exposed	2 / 329 (0.61%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	4 / 329 (1.22%)	2 / 132 (1.52%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	1 / 4	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	1 / 329 (0.30%)	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
Bradycardia			
subjects affected / exposed	1 / 329 (0.30%)	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
Nervous system disorders			
Haemorrhage intracranial			
subjects affected / exposed	1 / 329 (0.30%)	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	1 / 329 (0.30%)	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
Encephalopathy			
subjects affected / exposed	1 / 329 (0.30%)	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
Hepatic encephalopathy			
subjects affected / exposed	5 / 329 (1.52%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	1 / 6	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	2 / 329 (0.61%)	2 / 132 (1.52%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	0 / 329 (0.00%)	0 / 132 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Altered state of consciousness			
subjects affected / exposed	1 / 329 (0.30%)	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
Cerebrovascular accident			
subjects affected / exposed	2 / 329 (0.61%)	2 / 132 (1.52%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VIth nerve paralysis			
subjects affected / exposed	1 / 329 (0.30%)	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
VIth nerve disorder			

subjects affected / exposed	1 / 329 (0.30%)	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
Syncope			
subjects affected / exposed	1 / 329 (0.30%)	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
Subdural hygroma			
subjects affected / exposed	1 / 329 (0.30%)	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	1 / 329 (0.30%)	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	1 / 1	0 / 0	0 / 0
Metabolic encephalopathy			
subjects affected / exposed	0 / 329 (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	5 / 329 (1.52%)	3 / 132 (2.27%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	1 / 7	0 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune thrombocytopenia			
subjects affected / exposed	1 / 329 (0.30%)	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
Thrombocytopenia			
subjects affected / exposed	2 / 329 (0.61%)	1 / 132 (0.76%)	2 / 58 (3.45%)
occurrences causally related to treatment / all	3 / 4	3 / 3	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersplenism			

subjects affected / exposed	1 / 329 (0.30%)	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
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	1 / 329 (0.30%)	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
Eye disorders			
Blindness unilateral			
subjects affected / exposed	1 / 329 (0.30%)	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
Cataract			
subjects affected / exposed	1 / 329 (0.30%)	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
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	2 / 329 (0.61%)	2 / 132 (1.52%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	2 / 329 (0.61%)	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
Abdominal pain upper			
subjects affected / exposed	1 / 329 (0.30%)	2 / 132 (1.52%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	5 / 329 (1.52%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	3 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Ascites			
subjects affected / exposed	13 / 329 (3.95%)	6 / 132 (4.55%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	1 / 18	0 / 9	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	5 / 329 (1.52%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	3 / 5	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal fissure			
subjects affected / exposed	0 / 329 (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
Duodenal ulcer			
subjects affected / exposed	1 / 329 (0.30%)	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	2 / 329 (0.61%)	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
Gastric mucosal lesion			
subjects affected / exposed	1 / 329 (0.30%)	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
Gastrointestinal haemorrhage			
subjects affected / exposed	11 / 329 (3.34%)	3 / 132 (2.27%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	4 / 11	3 / 3	0 / 0
deaths causally related to treatment / all	1 / 3	1 / 1	0 / 0
Gastric ulcer perforation			
subjects affected / exposed	1 / 329 (0.30%)	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	1 / 1	0 / 0	0 / 0
Gastric varices haemorrhage			

subjects affected / exposed	4 / 329 (1.22%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	1 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 329 (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
Gastrointestinal necrosis			
subjects affected / exposed	1 / 329 (0.30%)	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
Haematemesis			
subjects affected / exposed	2 / 329 (0.61%)	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
Haemoperitoneum			
subjects affected / exposed	0 / 329 (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	1 / 329 (0.30%)	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
Ileus			
subjects affected / exposed	1 / 329 (0.30%)	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
Immune-mediated enterocolitis			
subjects affected / exposed	1 / 329 (0.30%)	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
Incarcerated umbilical hernia			

subjects affected / exposed	1 / 329 (0.30%)	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
Hiatus hernia			
subjects affected / exposed	1 / 329 (0.30%)	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
Melaena			
subjects affected / exposed	1 / 329 (0.30%)	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
Mesenteric vein thrombosis			
subjects affected / exposed	1 / 329 (0.30%)	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
Mouth haemorrhage			
subjects affected / exposed	1 / 329 (0.30%)	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
Oesophageal haemorrhage			
subjects affected / exposed	3 / 329 (0.91%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal stenosis			
subjects affected / exposed	1 / 329 (0.30%)	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
Varices oesophageal			
subjects affected / exposed	3 / 329 (0.91%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			

subjects affected / exposed	2 / 329 (0.61%)	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	3 / 329 (0.91%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			
subjects affected / exposed	1 / 329 (0.30%)	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
Upper gastrointestinal haemorrhage			
subjects affected / exposed	5 / 329 (1.52%)	5 / 132 (3.79%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	3 / 5	5 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Oesophageal varices haemorrhage			
subjects affected / exposed	10 / 329 (3.04%)	2 / 132 (1.52%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	3 / 12	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	2 / 329 (0.61%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diaphragmatic hernia			
subjects affected / exposed	1 / 329 (0.30%)	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
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 329 (0.30%)	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
Acute hepatic failure			

subjects affected / exposed	1 / 329 (0.30%)	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
Autoimmune hepatitis			
subjects affected / exposed	2 / 329 (0.61%)	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
Bile duct stone			
subjects affected / exposed	1 / 329 (0.30%)	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
Cholangitis			
subjects affected / exposed	4 / 329 (1.22%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug-induced liver injury			
subjects affected / exposed	0 / 329 (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 cirrhosis			
subjects affected / exposed	3 / 329 (0.91%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	4 / 329 (1.22%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Hepatic function abnormal			
subjects affected / exposed	1 / 329 (0.30%)	5 / 132 (3.79%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	1 / 1	5 / 5	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Hepatic pain			

subjects affected / exposed	1 / 329 (0.30%)	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
Hypertransaminasaemia			
subjects affected / exposed	1 / 329 (0.30%)	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
Hepatobiliary disease			
subjects affected / exposed	1 / 329 (0.30%)	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
Hepatorenal failure			
subjects affected / exposed	1 / 329 (0.30%)	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
Hepatorenal syndrome			
subjects affected / exposed	1 / 329 (0.30%)	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
Hyperbilirubinaemia			
subjects affected / exposed	3 / 329 (0.91%)	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
Hepatitis			
subjects affected / exposed	2 / 329 (0.61%)	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
Jaundice			
subjects affected / exposed	2 / 329 (0.61%)	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
Liver injury			

subjects affected / exposed	1 / 329 (0.30%)	1 / 132 (0.76%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Toxic skin eruption			
subjects affected / exposed	0 / 329 (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
Skin ulcer			
subjects affected / exposed	0 / 329 (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 eruption			
subjects affected / exposed	0 / 329 (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
Cutaneous vasculitis			
subjects affected / exposed	1 / 329 (0.30%)	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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 329 (0.91%)	1 / 132 (0.76%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	1 / 329 (0.30%)	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	0 / 329 (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	1 / 329 (0.30%)	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 failure			
subjects affected / exposed	0 / 329 (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
Nephropathy toxic			
subjects affected / exposed	1 / 329 (0.30%)	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
Proteinuria			
subjects affected / exposed	2 / 329 (0.61%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	1 / 329 (0.30%)	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
Endocrine disorders			
Hypophysitis			
subjects affected / exposed	2 / 329 (0.61%)	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
Addison's disease			
subjects affected / exposed	1 / 329 (0.30%)	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
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 329 (0.00%)	0 / 132 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Autoimmune arthritis			
subjects affected / exposed	1 / 329 (0.30%)	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
Back pain			
subjects affected / exposed	2 / 329 (0.61%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Groin pain			
subjects affected / exposed	1 / 329 (0.30%)	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
Muscular weakness			
subjects affected / exposed	1 / 329 (0.30%)	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
Myositis			
subjects affected / exposed	1 / 329 (0.30%)	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
Pathological fracture			
subjects affected / exposed	1 / 329 (0.30%)	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
Tendonitis			
subjects affected / exposed	1 / 329 (0.30%)	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
Infections and infestations			
Abscess limb			
subjects affected / exposed	1 / 329 (0.30%)	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
Escherichia sepsis			

subjects affected / exposed	1 / 329 (0.30%)	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
Bronchitis			
subjects affected / exposed	1 / 329 (0.30%)	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
Burkholderia pseudomallei infection			
subjects affected / exposed	1 / 329 (0.30%)	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
Cellulitis			
subjects affected / exposed	1 / 329 (0.30%)	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	1 / 329 (0.30%)	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
Empyema			
subjects affected / exposed	1 / 329 (0.30%)	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
Biliary tract infection			
subjects affected / exposed	1 / 329 (0.30%)	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
Gastroenteritis			
subjects affected / exposed	2 / 329 (0.61%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemophilus infection			

subjects affected / exposed	1 / 329 (0.30%)	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
Hepatitis E			
subjects affected / exposed	0 / 329 (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
Herpes simplex encephalitis			
subjects affected / exposed	1 / 329 (0.30%)	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
Lower respiratory tract infection			
subjects affected / exposed	1 / 329 (0.30%)	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
Sepsis			
subjects affected / exposed	8 / 329 (2.43%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	1 / 9	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	1 / 329 (0.30%)	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
Peritonsillar abscess			
subjects affected / exposed	0 / 329 (0.00%)	0 / 132 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	5 / 329 (1.52%)	3 / 132 (2.27%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	3 / 5	2 / 3	0 / 0
deaths causally related to treatment / all	1 / 2	0 / 1	0 / 0
Post procedural infection			

subjects affected / exposed	1 / 329 (0.30%)	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
Peritoneal abscess			
subjects affected / exposed	1 / 329 (0.30%)	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
Septic shock			
subjects affected / exposed	2 / 329 (0.61%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Skin infection			
subjects affected / exposed	1 / 329 (0.30%)	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
Tooth infection			
subjects affected / exposed	1 / 329 (0.30%)	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
Tuberculosis			
subjects affected / exposed	1 / 329 (0.30%)	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
Urinary tract infection			
subjects affected / exposed	3 / 329 (0.91%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 329 (0.30%)	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
Upper respiratory tract infection			

subjects affected / exposed	1 / 329 (0.30%)	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
COVID-19			
subjects affected / exposed	1 / 329 (0.30%)	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
Peritonitis bacterial			
subjects affected / exposed	1 / 329 (0.30%)	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
Pneumonia aspiration			
subjects affected / exposed	1 / 329 (0.30%)	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
Streptococcal bacteraemia			
subjects affected / exposed	1 / 329 (0.30%)	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
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	2 / 329 (0.61%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemic hyperosmolar nonketotic syndrome			
subjects affected / exposed	1 / 329 (0.30%)	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
Hyperglycaemia			
subjects affected / exposed	3 / 329 (0.91%)	0 / 132 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hyperammonaemia			

subjects affected / exposed	1 / 329 (0.30%)	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
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 329 (0.30%)	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
Diabetes mellitus			
subjects affected / exposed	1 / 329 (0.30%)	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
Decreased appetite			
subjects affected / exposed	1 / 329 (0.30%)	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
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 329 (0.30%)	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
Metabolic acidosis			
subjects affected / exposed	1 / 329 (0.30%)	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
Lactic acidosis			
subjects affected / exposed	1 / 329 (0.30%)	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
Hyponatraemia			
subjects affected / exposed	1 / 329 (0.30%)	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
Hypokalaemia			

subjects affected / exposed	1 / 329 (0.30%)	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
Hypoglycaemia			
subjects affected / exposed	2 / 329 (0.61%)	1 / 132 (0.76%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoalbuminaemia			
subjects affected / exposed	0 / 329 (0.00%)	0 / 132 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoproteinaemia			
subjects affected / exposed	1 / 329 (0.30%)	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

Serious adverse events	Sorafenib - Global		
Total subjects affected by serious adverse events			
subjects affected / exposed	51 / 156 (32.69%)		
number of deaths (all causes)	114		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Oesophageal squamous cell carcinoma			
subjects affected / exposed	0 / 156 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neoplasm			
subjects affected / exposed	0 / 156 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chronic myeloid leukaemia			
subjects affected / exposed	0 / 156 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Gastric cancer				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tumour haemorrhage				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tumour rupture				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Bleeding varicose vein				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Deep vein thrombosis				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Embolism				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemorrhage				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypertension				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Thrombosis				

subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Phlebitis				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypotension				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peripheral vascular disorder				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Death				
subjects affected / exposed	2 / 156 (1.28%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Fatigue				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Multiple organ dysfunction syndrome				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyrexia				

subjects affected / exposed	2 / 156 (1.28%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Oedema peripheral				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Anaphylactic reaction				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cytokine release syndrome				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Pelvic pain				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Scrotal dermatitis				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Chronic obstructive pulmonary disease				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Asthma				

subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemoptysis				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	2 / 156 (1.28%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Epistaxis				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary haemorrhage				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	2 / 156 (1.28%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				

subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hiccups				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary hypertension				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory distress				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acute pulmonary oedema				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cough				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Orthopnoea				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Mental status changes				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Delirium				

subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Confusional state				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				
Alanine aminotransferase increased				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Amylase increased				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Aspartate aminotransferase increased				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood bilirubin increased				
subjects affected / exposed	2 / 156 (1.28%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
General physical condition abnormal				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Granulocyte count decreased				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lipase increased				

subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Platelet count decreased				
subjects affected / exposed	0 / 156 (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	1 / 156 (0.64%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Fall				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Acetabulum fracture				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Compression fracture				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hip fracture				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Humerus fracture				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infusion related reaction				

subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pelvic fracture				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal compression fracture				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subdural haematoma				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Toxicity to various agents				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Congenital, familial and genetic disorders				
Hydrocele				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute coronary syndrome				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			

Atrial fibrillation				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Acute myocardial infarction				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure congestive				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bradycardia				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Haemorrhage intracranial				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Epilepsy				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Encephalopathy				

subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic encephalopathy				
subjects affected / exposed	3 / 156 (1.92%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Cerebral infarction				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebral haemorrhage				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Altered state of consciousness				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
VIth nerve paralysis				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
VIth nerve disorder				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Syncope				

subjects affected / exposed	0 / 156 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Subdural hygroma			
subjects affected / exposed	0 / 156 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 156 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolic encephalopathy			
subjects affected / exposed	1 / 156 (0.64%)		
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	2 / 156 (1.28%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Immune thrombocytopenia			
subjects affected / exposed	0 / 156 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	2 / 156 (1.28%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Hypersplenism			
subjects affected / exposed	0 / 156 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			

Hypoacusis			
subjects affected / exposed	0 / 156 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Blindness unilateral			
subjects affected / exposed	0 / 156 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cataract			
subjects affected / exposed	0 / 156 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 156 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	2 / 156 (1.28%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Abdominal pain upper			
subjects affected / exposed	0 / 156 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 156 (0.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ascites			
subjects affected / exposed	1 / 156 (0.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Colitis				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Anal fissure				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Duodenal ulcer				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Dysphagia				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastric mucosal lesion				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	3 / 156 (1.92%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Gastric ulcer perforation				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastric varices haemorrhage				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastric ulcer haemorrhage				

subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal necrosis				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haematemesis				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemoperitoneum				
subjects affected / exposed	2 / 156 (1.28%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 1			
Large intestinal haemorrhage				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Immune-mediated enterocolitis				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Incarcerated umbilical hernia				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hiatus hernia				

subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Melaena				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Mesenteric vein thrombosis				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Mouth haemorrhage				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oesophageal haemorrhage				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oesophageal stenosis				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Varices oesophageal				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	2 / 156 (1.28%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage				

subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Umbilical hernia				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper gastrointestinal haemorrhage				
subjects affected / exposed	2 / 156 (1.28%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Oesophageal varices haemorrhage				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diaphragmatic hernia				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholecystitis				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acute hepatic failure				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Autoimmune hepatitis				

subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bile duct stone				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholangitis				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Drug-induced liver injury				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic cirrhosis				
subjects affected / exposed	2 / 156 (1.28%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	1 / 2			
Hepatic failure				
subjects affected / exposed	2 / 156 (1.28%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Hepatic function abnormal				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic pain				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypertransaminasaemia				

subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disease				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatorenal failure				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatorenal syndrome				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyperbilirubinaemia				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatitis				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Jaundice				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Liver injury				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Toxic skin eruption				

subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Skin ulcer				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Drug eruption				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cutaneous vasculitis				
subjects affected / exposed	0 / 156 (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	2 / 156 (1.28%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Haematuria				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal haematoma				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nephritis				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal failure				

subjects affected / exposed	1 / 156 (0.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nephropathy toxic			
subjects affected / exposed	0 / 156 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Proteinuria			
subjects affected / exposed	0 / 156 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal impairment			
subjects affected / exposed	0 / 156 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Hypophysitis			
subjects affected / exposed	0 / 156 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Addison's disease			
subjects affected / exposed	0 / 156 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 156 (0.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Autoimmune arthritis			
subjects affected / exposed	0 / 156 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Back pain				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Groin pain				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Muscular weakness				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myositis				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pathological fracture				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tendonitis				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Abscess limb				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Escherichia sepsis				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchitis				

subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Burkholderia pseudomallei infection				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Device related infection				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Empyema				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Biliary tract infection				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemophilus infection				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatitis E				

subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Herpes simplex encephalitis				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peritonitis				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peritonsillar abscess				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Post procedural infection				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peritoneal abscess				

subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin infection				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tooth infection				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tuberculosis				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
COVID-19				

subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peritonitis bacterial				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Streptococcal bacteraemia				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Hyperkalaemia				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyperglycaemic hyperosmolar nonketotic syndrome				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyperglycaemia				
subjects affected / exposed	1 / 156 (0.64%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hyperammonaemia				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diabetes mellitus inadequate control				

subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diabetes mellitus				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Decreased appetite				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Type 2 diabetes mellitus				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolic acidosis				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lactic acidosis				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyponatraemia				
subjects affected / exposed	2 / 156 (1.28%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Hypokalaemia				
subjects affected / exposed	0 / 156 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypoglycaemia				

subjects affected / exposed	1 / 156 (0.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoalbuminaemia			
subjects affected / exposed	1 / 156 (0.64%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoproteinaemia			
subjects affected / exposed	0 / 156 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Atezolizumab + Bevacizumab - Global	Atezolizumab + Bevacizumab - China	Sorafenib - China
Total subjects affected by non-serious adverse events			
subjects affected / exposed	311 / 329 (94.53%)	129 / 132 (97.73%)	55 / 58 (94.83%)
Vascular disorders			
Hypertension			
subjects affected / exposed	118 / 329 (35.87%)	54 / 132 (40.91%)	12 / 58 (20.69%)
occurrences (all)	191	90	15
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	28 / 329 (8.51%)	11 / 132 (8.33%)	3 / 58 (5.17%)
occurrences (all)	40	12	3
Fatigue			
subjects affected / exposed	76 / 329 (23.10%)	17 / 132 (12.88%)	6 / 58 (10.34%)
occurrences (all)	92	22	6
Oedema peripheral			
subjects affected / exposed	45 / 329 (13.68%)	13 / 132 (9.85%)	3 / 58 (5.17%)
occurrences (all)	55	18	3
Pyrexia			
subjects affected / exposed	58 / 329 (17.63%)	23 / 132 (17.42%)	6 / 58 (10.34%)
occurrences (all)	83	32	9

Malaise			
subjects affected / exposed	13 / 329 (3.95%)	6 / 132 (4.55%)	3 / 58 (5.17%)
occurrences (all)	13	6	3
Pain			
subjects affected / exposed	9 / 329 (2.74%)	9 / 132 (6.82%)	1 / 58 (1.72%)
occurrences (all)	10	10	1
Respiratory, thoracic and mediastinal disorders			
Dysphonia			
subjects affected / exposed	31 / 329 (9.42%)	6 / 132 (4.55%)	3 / 58 (5.17%)
occurrences (all)	35	6	3
Cough			
subjects affected / exposed	46 / 329 (13.98%)	14 / 132 (10.61%)	5 / 58 (8.62%)
occurrences (all)	56	19	6
Dyspnoea			
subjects affected / exposed	28 / 329 (8.51%)	5 / 132 (3.79%)	2 / 58 (3.45%)
occurrences (all)	29	5	2
Epistaxis			
subjects affected / exposed	37 / 329 (11.25%)	12 / 132 (9.09%)	2 / 58 (3.45%)
occurrences (all)	45	12	2
Haemoptysis			
subjects affected / exposed	4 / 329 (1.22%)	1 / 132 (0.76%)	3 / 58 (5.17%)
occurrences (all)	4	1	3
Psychiatric disorders			
Insomnia			
subjects affected / exposed	39 / 329 (11.85%)	11 / 132 (8.33%)	5 / 58 (8.62%)
occurrences (all)	41	12	5
Investigations			
Platelet count decreased			
subjects affected / exposed	48 / 329 (14.59%)	27 / 132 (20.45%)	10 / 58 (17.24%)
occurrences (all)	87	65	11
Alanine aminotransferase increased			
subjects affected / exposed	56 / 329 (17.02%)	30 / 132 (22.73%)	12 / 58 (20.69%)
occurrences (all)	80	52	18
Aspartate aminotransferase increased			
subjects affected / exposed	77 / 329 (23.40%)	41 / 132 (31.06%)	19 / 58 (32.76%)
occurrences (all)	116	76	23

Blood alkaline phosphatase increased			
subjects affected / exposed	33 / 329 (10.03%)	19 / 132 (14.39%)	7 / 58 (12.07%)
occurrences (all)	43	29	9
Blood bilirubin increased			
subjects affected / exposed	59 / 329 (17.93%)	35 / 132 (26.52%)	14 / 58 (24.14%)
occurrences (all)	114	86	16
Blood creatinine increased			
subjects affected / exposed	20 / 329 (6.08%)	10 / 132 (7.58%)	0 / 58 (0.00%)
occurrences (all)	32	18	0
Weight decreased			
subjects affected / exposed	50 / 329 (15.20%)	21 / 132 (15.91%)	6 / 58 (10.34%)
occurrences (all)	55	23	9
White blood cell count decreased			
subjects affected / exposed	21 / 329 (6.38%)	23 / 132 (17.42%)	9 / 58 (15.52%)
occurrences (all)	76	83	15
Gamma-glutamyltransferase increased			
subjects affected / exposed	11 / 329 (3.34%)	16 / 132 (12.12%)	9 / 58 (15.52%)
occurrences (all)	13	18	9
Blood thyroid stimulating hormone increased			
subjects affected / exposed	10 / 329 (3.04%)	11 / 132 (8.33%)	0 / 58 (0.00%)
occurrences (all)	16	15	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	10 / 329 (3.04%)	10 / 132 (7.58%)	9 / 58 (15.52%)
occurrences (all)	14	13	13
Blood bilirubin unconjugated increased			
subjects affected / exposed	7 / 329 (2.13%)	7 / 132 (5.30%)	2 / 58 (3.45%)
occurrences (all)	19	19	2
Bilirubin conjugated increased			
subjects affected / exposed	12 / 329 (3.65%)	13 / 132 (9.85%)	6 / 58 (10.34%)
occurrences (all)	28	29	10
Lymphocyte count decreased			
subjects affected / exposed	15 / 329 (4.56%)	9 / 132 (6.82%)	3 / 58 (5.17%)
occurrences (all)	25	17	5
Neutrophil count decreased			

subjects affected / exposed	16 / 329 (4.86%)	18 / 132 (13.64%)	5 / 58 (8.62%)
occurrences (all)	46	56	6
Protein urine present			
subjects affected / exposed	3 / 329 (0.91%)	5 / 132 (3.79%)	5 / 58 (8.62%)
occurrences (all)	5	9	5
Prothrombin time prolonged			
subjects affected / exposed	6 / 329 (1.82%)	7 / 132 (5.30%)	1 / 58 (1.72%)
occurrences (all)	7	10	1
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	33 / 329 (10.03%)	13 / 132 (9.85%)	0 / 58 (0.00%)
occurrences (all)	40	13	0
Nervous system disorders			
Headache			
subjects affected / exposed	35 / 329 (10.64%)	14 / 132 (10.61%)	2 / 58 (3.45%)
occurrences (all)	44	18	4
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	38 / 329 (11.55%)	26 / 132 (19.70%)	8 / 58 (13.79%)
occurrences (all)	56	44	9
Thrombocytopenia			
subjects affected / exposed	32 / 329 (9.73%)	22 / 132 (16.67%)	5 / 58 (8.62%)
occurrences (all)	45	41	5
Neutropenia			
subjects affected / exposed	20 / 329 (6.08%)	12 / 132 (9.09%)	3 / 58 (5.17%)
occurrences (all)	28	20	6
Leukopenia			
subjects affected / exposed	21 / 329 (6.38%)	19 / 132 (14.39%)	4 / 58 (6.90%)
occurrences (all)	33	32	6
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	31 / 329 (9.42%)	9 / 132 (6.82%)	2 / 58 (3.45%)
occurrences (all)	36	10	3
Constipation			
subjects affected / exposed	58 / 329 (17.63%)	18 / 132 (13.64%)	5 / 58 (8.62%)
occurrences (all)	63	20	5

Diarrhoea			
subjects affected / exposed	75 / 329 (22.80%)	20 / 132 (15.15%)	26 / 58 (44.83%)
occurrences (all)	109	28	38
Nausea			
subjects affected / exposed	49 / 329 (14.89%)	18 / 132 (13.64%)	7 / 58 (12.07%)
occurrences (all)	64	22	9
Stomatitis			
subjects affected / exposed	19 / 329 (5.78%)	4 / 132 (3.03%)	2 / 58 (3.45%)
occurrences (all)	21	4	2
Abdominal pain upper			
subjects affected / exposed	20 / 329 (6.08%)	7 / 132 (5.30%)	4 / 58 (6.90%)
occurrences (all)	30	8	4
Abdominal pain			
subjects affected / exposed	50 / 329 (15.20%)	19 / 132 (14.39%)	10 / 58 (17.24%)
occurrences (all)	63	24	15
Abdominal distension			
subjects affected / exposed	26 / 329 (7.90%)	16 / 132 (12.12%)	4 / 58 (6.90%)
occurrences (all)	27	17	4
Vomiting			
subjects affected / exposed	34 / 329 (10.33%)	15 / 132 (11.36%)	5 / 58 (8.62%)
occurrences (all)	49	25	5
Gingival bleeding			
subjects affected / exposed	11 / 329 (3.34%)	9 / 132 (6.82%)	1 / 58 (1.72%)
occurrences (all)	14	12	1
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	8 / 329 (2.43%)	8 / 132 (6.06%)	3 / 58 (5.17%)
occurrences (all)	8	9	3
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	71 / 329 (21.58%)	24 / 132 (18.18%)	7 / 58 (12.07%)
occurrences (all)	99	31	8
Alopecia			
subjects affected / exposed	6 / 329 (1.82%)	2 / 132 (1.52%)	7 / 58 (12.07%)
occurrences (all)	6	2	7
Palmar-plantar erythrodysaesthesia syndrome			

subjects affected / exposed	6 / 329 (1.82%)	2 / 132 (1.52%)	33 / 58 (56.90%)
occurrences (all)	7	2	39
Rash			
subjects affected / exposed	46 / 329 (13.98%)	21 / 132 (15.91%)	7 / 58 (12.07%)
occurrences (all)	51	24	7
Rash maculo-papular			
subjects affected / exposed	10 / 329 (3.04%)	3 / 132 (2.27%)	3 / 58 (5.17%)
occurrences (all)	11	3	4
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	107 / 329 (32.52%)	68 / 132 (51.52%)	11 / 58 (18.97%)
occurrences (all)	184	120	18
Haematuria			
subjects affected / exposed	13 / 329 (3.95%)	8 / 132 (6.06%)	0 / 58 (0.00%)
occurrences (all)	25	19	0
Cylindruria			
subjects affected / exposed	7 / 329 (2.13%)	8 / 132 (6.06%)	0 / 58 (0.00%)
occurrences (all)	20	21	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	35 / 329 (10.64%)	15 / 132 (11.36%)	1 / 58 (1.72%)
occurrences (all)	41	19	1
Hyperthyroidism			
subjects affected / exposed	17 / 329 (5.17%)	9 / 132 (6.82%)	0 / 58 (0.00%)
occurrences (all)	20	11	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	62 / 329 (18.84%)	16 / 132 (12.12%)	1 / 58 (1.72%)
occurrences (all)	73	18	1
Back pain			
subjects affected / exposed	27 / 329 (8.21%)	11 / 132 (8.33%)	5 / 58 (8.62%)
occurrences (all)	30	11	7
Myalgia			
subjects affected / exposed	20 / 329 (6.08%)	4 / 132 (3.03%)	2 / 58 (3.45%)
occurrences (all)	24	4	2
Pain in extremity			

subjects affected / exposed	10 / 329 (3.04%)	3 / 132 (2.27%)	3 / 58 (5.17%)
occurrences (all)	10	3	3
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	20 / 329 (6.08%)	7 / 132 (5.30%)	1 / 58 (1.72%)
occurrences (all)	26	10	1
Upper respiratory tract infection			
subjects affected / exposed	24 / 329 (7.29%)	22 / 132 (16.67%)	2 / 58 (3.45%)
occurrences (all)	27	26	2
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	68 / 329 (20.67%)	27 / 132 (20.45%)	12 / 58 (20.69%)
occurrences (all)	78	32	15
Hyperglycaemia			
subjects affected / exposed	23 / 329 (6.99%)	13 / 132 (9.85%)	0 / 58 (0.00%)
occurrences (all)	40	30	0
Hypoalbuminaemia			
subjects affected / exposed	42 / 329 (12.77%)	32 / 132 (24.24%)	5 / 58 (8.62%)
occurrences (all)	53	44	8
Hypokalaemia			
subjects affected / exposed	13 / 329 (3.95%)	13 / 132 (9.85%)	11 / 58 (18.97%)
occurrences (all)	19	22	13
Hyponatraemia			
subjects affected / exposed	26 / 329 (7.90%)	9 / 132 (6.82%)	4 / 58 (6.90%)
occurrences (all)	32	16	4
Hypophosphataemia			
subjects affected / exposed	9 / 329 (2.74%)	3 / 132 (2.27%)	6 / 58 (10.34%)
occurrences (all)	10	6	10
Hypoproteinaemia			
subjects affected / exposed	4 / 329 (1.22%)	8 / 132 (6.06%)	1 / 58 (1.72%)
occurrences (all)	4	10	1

Non-serious adverse events	Sorafenib - Global		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	147 / 156 (94.23%)		
Vascular disorders			

Hypertension			
subjects affected / exposed	38 / 156 (24.36%)		
occurrences (all)	43		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	21 / 156 (13.46%)		
occurrences (all)	23		
Fatigue			
subjects affected / exposed	30 / 156 (19.23%)		
occurrences (all)	32		
Oedema peripheral			
subjects affected / exposed	6 / 156 (3.85%)		
occurrences (all)	6		
Pyrexia			
subjects affected / exposed	15 / 156 (9.62%)		
occurrences (all)	22		
Malaise			
subjects affected / exposed	5 / 156 (3.21%)		
occurrences (all)	5		
Pain			
subjects affected / exposed	1 / 156 (0.64%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Dysphonia			
subjects affected / exposed	11 / 156 (7.05%)		
occurrences (all)	11		
Cough			
subjects affected / exposed	15 / 156 (9.62%)		
occurrences (all)	18		
Dyspnoea			
subjects affected / exposed	5 / 156 (3.21%)		
occurrences (all)	5		
Epistaxis			
subjects affected / exposed	6 / 156 (3.85%)		
occurrences (all)	6		
Haemoptysis			

subjects affected / exposed	4 / 156 (2.56%)		
occurrences (all)	4		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	11 / 156 (7.05%)		
occurrences (all)	11		
Investigations			
Platelet count decreased			
subjects affected / exposed	18 / 156 (11.54%)		
occurrences (all)	22		
Alanine aminotransferase increased			
subjects affected / exposed	14 / 156 (8.97%)		
occurrences (all)	18		
Aspartate aminotransferase increased			
subjects affected / exposed	28 / 156 (17.95%)		
occurrences (all)	32		
Blood alkaline phosphatase increased			
subjects affected / exposed	11 / 156 (7.05%)		
occurrences (all)	12		
Blood bilirubin increased			
subjects affected / exposed	23 / 156 (14.74%)		
occurrences (all)	27		
Blood creatinine increased			
subjects affected / exposed	1 / 156 (0.64%)		
occurrences (all)	1		
Weight decreased			
subjects affected / exposed	15 / 156 (9.62%)		
occurrences (all)	18		
White blood cell count decreased			
subjects affected / exposed	9 / 156 (5.77%)		
occurrences (all)	24		
Gamma-glutamyltransferase increased			
subjects affected / exposed	7 / 156 (4.49%)		
occurrences (all)	7		
Blood thyroid stimulating hormone increased			

subjects affected / exposed	0 / 156 (0.00%)		
occurrences (all)	0		
Blood lactate dehydrogenase increased			
subjects affected / exposed	7 / 156 (4.49%)		
occurrences (all)	10		
Blood bilirubin unconjugated increased			
subjects affected / exposed	1 / 156 (0.64%)		
occurrences (all)	1		
Bilirubin conjugated increased			
subjects affected / exposed	4 / 156 (2.56%)		
occurrences (all)	7		
Lymphocyte count decreased			
subjects affected / exposed	2 / 156 (1.28%)		
occurrences (all)	4		
Neutrophil count decreased			
subjects affected / exposed	5 / 156 (3.21%)		
occurrences (all)	15		
Protein urine present			
subjects affected / exposed	4 / 156 (2.56%)		
occurrences (all)	4		
Prothrombin time prolonged			
subjects affected / exposed	1 / 156 (0.64%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	0 / 156 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 156 (7.05%)		
occurrences (all)	14		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	14 / 156 (8.97%)		
occurrences (all)	15		

Thrombocytopenia			
subjects affected / exposed	7 / 156 (4.49%)		
occurrences (all)	9		
Neutropenia			
subjects affected / exposed	4 / 156 (2.56%)		
occurrences (all)	7		
Leukopenia			
subjects affected / exposed	4 / 156 (2.56%)		
occurrences (all)	6		
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	8 / 156 (5.13%)		
occurrences (all)	10		
Constipation			
subjects affected / exposed	25 / 156 (16.03%)		
occurrences (all)	27		
Diarrhoea			
subjects affected / exposed	79 / 156 (50.64%)		
occurrences (all)	107		
Nausea			
subjects affected / exposed	25 / 156 (16.03%)		
occurrences (all)	28		
Stomatitis			
subjects affected / exposed	7 / 156 (4.49%)		
occurrences (all)	7		
Abdominal pain upper			
subjects affected / exposed	9 / 156 (5.77%)		
occurrences (all)	10		
Abdominal pain			
subjects affected / exposed	27 / 156 (17.31%)		
occurrences (all)	31		
Abdominal distension			
subjects affected / exposed	5 / 156 (3.21%)		
occurrences (all)	5		
Vomiting			

subjects affected / exposed	14 / 156 (8.97%)		
occurrences (all)	14		
Gingival bleeding			
subjects affected / exposed	0 / 156 (0.00%)		
occurrences (all)	0		
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	4 / 156 (2.56%)		
occurrences (all)	4		
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	15 / 156 (9.62%)		
occurrences (all)	16		
Alopecia			
subjects affected / exposed	22 / 156 (14.10%)		
occurrences (all)	22		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	76 / 156 (48.72%)		
occurrences (all)	82		
Rash			
subjects affected / exposed	28 / 156 (17.95%)		
occurrences (all)	28		
Rash maculo-papular			
subjects affected / exposed	5 / 156 (3.21%)		
occurrences (all)	6		
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	13 / 156 (8.33%)		
occurrences (all)	19		
Haematuria			
subjects affected / exposed	0 / 156 (0.00%)		
occurrences (all)	0		
Cylindruria			
subjects affected / exposed	0 / 156 (0.00%)		
occurrences (all)	0		
Endocrine disorders			

Hypothyroidism subjects affected / exposed occurrences (all)	3 / 156 (1.92%) 3		
Hyperthyroidism subjects affected / exposed occurrences (all)	0 / 156 (0.00%) 0		
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	9 / 156 (5.77%) 10		
Back pain subjects affected / exposed occurrences (all)	6 / 156 (3.85%) 6		
Myalgia subjects affected / exposed occurrences (all)	5 / 156 (3.21%) 6		
Pain in extremity subjects affected / exposed occurrences (all)	6 / 156 (3.85%) 6		
Infections and infestations			
Nasopharyngitis subjects affected / exposed occurrences (all)	4 / 156 (2.56%) 4		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 156 (1.28%) 2		
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	39 / 156 (25.00%) 50		
Hyperglycaemia subjects affected / exposed occurrences (all)	4 / 156 (2.56%) 5		
Hypoalbuminaemia subjects affected / exposed occurrences (all)	11 / 156 (7.05%) 13		

Hypokalaemia subjects affected / exposed occurrences (all)	11 / 156 (7.05%) 13		
Hyponatraemia subjects affected / exposed occurrences (all)	7 / 156 (4.49%) 7		
Hypophosphataemia subjects affected / exposed occurrences (all)	11 / 156 (7.05%) 13		
Hypoproteinaemia subjects affected / exposed occurrences (all)	1 / 156 (0.64%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 March 2018	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.
15 September 2018	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.

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