Clinical trial results:
A Phase III, Multicenter, Randomized, Open-Label Study of Atezolizumab (Anti-PD-L1 Antibody) Plus Bevacizumab Versus Active Surveillance as Adjuvant Therapy in Patients With Hepatocellular Carcinoma at High Risk of Recurrence After Surgical Resection or Ablation

Summary

EudraCT number	2019-002491-14
Trial protocol	DE CZ FR ES PL NL BE IT
Global end of trial date	

Results information

Result version number	v1 (current)
This version publication date	29 September 2023
First version publication date	29 September 2023

Trial information

Trial identification

Sponsor protocol code	WO41535

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04102098
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	Medical Communications, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	21 October 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 October 2022
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

IMbrave050 is an ongoing study designed to evaluate the efficacy and safety of adjuvant therapy with atezolizumab plus bevacizumab compared with active surveillance in participants with completely resected or ablated hepatocellular carcinoma (HCC) who are at high risk for disease recurrence.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 December 2019
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	79 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	Austria: 8
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Brazil: 8
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	China: 294
Country: Number of subjects enrolled	Costa Rica: 1
Country: Number of subjects enrolled	Czechia: 4
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	France: 37
Country: Number of subjects enrolled	Hong Kong: 7
Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	Japan: 61
Country: Number of subjects enrolled	Korea, Republic of: 125
Country: Number of subjects enrolled	Mexico: 4
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	New Zealand: 5
Country: Number of subjects enrolled	Peru: 4
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Russian Federation: 14

Country: Number of subjects enrolled	Singapore: 6
Country: Number of subjects enrolled	Thailand: 15
Country: Number of subjects enrolled	Turkey: 1
Country: Number of subjects enrolled	Taiwan: 28
Country: Number of subjects enrolled	United States: 19
Worldwide total number of subjects	668
EEA total number of subjects	72

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)	427
From 65 to 84 years	239
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 134 centers in 26 countries/regions.

Pre-assignment

Screening details:

Participants included completely resected or ablated hepatocellular carcinoma (HCC) who are at high risk for disease recurrence.

Participants randomized to Active Surveillance arm were offered the option to crossover to receive treatment with Atezolizumab.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm B (active surveillance)

Arm description:

Active surveillance of participants.

Arm type	Active surveillance

No investigational medicinal product assigned in this arm

Arm title	Arm A (atezolizumab plus bevacizumab)

Arm description:

Participants received Atezolizumab + Bevacizumab until disease recurrence or unacceptable toxicity.

Arm type	Experimental
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	Avastin
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab will be administered by IV infusion at a dose of 15 mg/kg on Day 1 of each 21-day cycle.

Investigational medicinal product name	Atezolizumab
Investigational medicinal product code	
Other name	Tecentriq
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Atezolizumab 1200 mg will be administered by IV infusion on Day 1 of each 21-day cycle.

Number of subjects in period 1	Arm B (active surveillance)	Arm A (atezolizumab plus bevacizumab)
Started	334	334
Completed	0	0
Not completed	334	334
Physician Decision	-	1
Ongoing in study	302	291
Death	20	27
Withdrawal by Subject	11	14
Lost to follow-up	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Arm B (active surveillance)
Reporting group description:	
Active surveillance of participants.	
Reporting group title	Arm A (atezolizumab plus bevacizumab)
Reporting group description:	
Participants received Atezolizumab + Bevacizumab until disease recurrence or unacceptable toxicity.	

Reporting group values	Arm B (active surveillance)	Arm A (atezolizumab plus bevacizumab)	Total
Number of subjects	334	334	668
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	215	212	427
From 65-84 years	118	121	239
85 years and over	1	1	2
Age Continuous Units: Years			
arithmetic mean	58.9	59.0	
standard deviation	± 12.5	± 12.1	-
Sex: Female, Male Units: Participants			
Female	56	57	113
Male	278	277	555
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	3	4
Asian	269	276	545
Native Hawaiian or Other Pacific Islander	1	0	1
Black or African American	1	2	3
White	41	35	76
More than one race	0	2	2
Unknown or Not Reported	21	16	37

End points

End points reporting groups

Reporting group title	Arm B (active surveillance)
Reporting group description: Active surveillance of participants.	
Reporting group title	Arm A (atezolizumab plus bevacizumab)
Reporting group description: Participants received Atezolizumab + Bevacizumab until disease recurrence or unacceptable toxicity.	

Primary: Recurrence-Free Survival (RFS), as Determined by IRF

End point title	Recurrence-Free Survival (RFS), as Determined by IRF
End point description: RFS is defined as the time from randomization to the first documented occurrence of intrahepatic or extrahepatic HCC as determined by an IRF, or death from any cause (whichever occurs first). Note: 999999 = not estimable.	
End point type	Primary
End point timeframe: Baseline up to approximately 33 months	

End point values	Arm B (active surveillance)	Arm A (atezolizumab plus bevacizumab)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	334	334		
Units: Months				
median (confidence interval 95%)	999999 (21.4 to 999999)	999999 (22.1 to 999999)		

Statistical analyses

Statistical analysis title	RFS as Determined by IRF Statistical Analysis
Statistical analysis description: Stratification factors include geographic region (Asia Pacific excluding Japan vs. rest of world) and High risk features/curative procedure (Ablation vs. Resection with 1 high risk feature vs. Resection with 2 or more high risk features).	
Comparison groups	Arm B (active surveillance) v Arm A (atezolizumab plus bevacizumab)
Number of subjects included in analysis	668
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.012
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.72

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	0.93

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS is defined as the time from randomization to death from any cause.

End point type	Secondary

End point timeframe:

Baseline up to approximately 91 months

End point values	Arm B (active surveillance)	Arm A (atezolizumab plus bevacizumab)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[1]	0[2]		
Units: Months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[1] - To be reported after end of study.

[2] - To be reported after end of study.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Recurrence (TTR)

End point title	Time to Recurrence (TTR)

End point description:

TTR defined as the time from
randomization to first documented occurrence of intrahepatic or extrahepatic HCC, as determined by the investigator and by an IRF.

End point type	Secondary

End point timeframe:

Baseline up to approximately 91 months

End point values	Arm B (active surveillance)	Arm A (atezolizumab plus bevacizumab)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[3]	0[4]		
Units: Months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[3] - To be reported after end of study.

[4] - To be reported after end of study.

Statistical analyses

No statistical analyses for this end point

Secondary: RFS Rate at 24 and 36 Months, as Assessed by the IRF

End point title	RFS Rate at 24 and 36 Months, as Assessed by the IRF

End point description:

End point type	Secondary

End point timeframe:

Randomization up to 24 months and up to 36 months

End point values	Arm B (active surveillance)	Arm A (atezolizumab plus bevacizumab)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[5]	0[6]		
Units: Months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[5] - To be reported after end of study.

[6] - To be reported after end of study.

Statistical analyses

No statistical analyses for this end point

Secondary: RFS as Determined by the Investigator

End point title	RFS as Determined by the Investigator

End point description:

RFS is defined as the time from randomization to the first documented occurrence of intrahepatic or extrahepatic HCC as determined by an investigator, or death from any cause (whichever occurs first).

End point type	Secondary

End point timeframe:

Baseline up to approximately 91 months

End point values	Arm B (active surveillance)	Arm A (atezolizumab plus bevacizumab)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[7]	0[8]		
Units: Months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[7] - To be reported after end of study.

[8] - To be reported after end of study.

Statistical analyses

No statistical analyses for this end point

Secondary: RFS Rate at 24 and 36 Months, as Assessed by the Investigator

End point title	RFS Rate at 24 and 36 Months, as Assessed by the Investigator

End point description:

End point type	Secondary

End point timeframe:

Randomization up to 24 months and up to 36 months

End point values	Arm B (active surveillance)	Arm A (atezolizumab plus bevacizumab)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[9]	0[10]		
Units: Months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[9] - To be reported after end of study.

[10] - To be reported after end of study.

Statistical analyses

No statistical analyses for this end point

Secondary: OS Rate at 24 and 36 Months

End point title	OS Rate at 24 and 36 Months

End point description:

OS rate defined as the proportion of patients who have not experienced death from any cause at 24 and 36 months after randomization.

End point type	Secondary

End point timeframe:

Baseline to 24 and 36 months

End point values	Arm B (active surveillance)	Arm A (atezolizumab plus bevacizumab)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[11]	0[12]		
Units: Months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[11] - To be reported after end of study.

[12] - To be reported after end of study.

Statistical analyses

No statistical analyses for this end point

Secondary: RFS in Pd-L1-High Subgroup

End point title	RFS in Pd-L1-High Subgroup

End point description:

RFS after randomization as determined by the investigator and by an IRF, among patients in the PD-L1-high subgroup.

End point type	Secondary

End point timeframe:

Baseline up to approximately 91 months

End point values	Arm B (active surveillance)	Arm A (atezolizumab plus bevacizumab)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[13]	0[14]		
Units: Months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[13] - To be reported after end of study.

[14] - To be reported after end of study.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Extrahepatic Spread (EHS) or Macrovascular Invasion

End point title	Time to Extrahepatic Spread (EHS) or Macrovascular Invasion

End point description:

Time to EHS or macrovascular invasion after randomization, defined as the time from randomization to the first appearance of EHS or macrovascular invasion, as determined by the investigator.

End point type	Secondary

End point timeframe:

Baseline up to approximately 91 months

End point values	Arm B (active surveillance)	Arm A (atezolizumab plus bevacizumab)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[15]	0[16]		
Units: Months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[15] - To be reported after end of study.

[16] - To be reported after end of study.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Adverse Events

End point title	Percentage of Participants With Adverse Events

End point description:

End point type	Secondary

End point timeframe:

Baseline up to approximately 91 months

End point values	Arm B (active surveillance)	Arm A (atezolizumab plus bevacizumab)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[17]	0[18]		
Units: Percentage of particiapnts				
number (not applicable)				

Notes:

[17] - To be reported after end of study.

[18] - To be reported after end of study.

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Concentration of Atezolizumab

End point title	Serum Concentration of Atezolizumab[19]

End point description:

Serum concentration of atezolizumab. Note: 99999=not estimable.

End point type	Secondary

End point timeframe:

Prior to any drug administration on Day 1 of Cycles 1, 2, 3, 4, 8, 12, and 16, and 30 minutes after end of atezolizumab infusion on Day 1 of Cycle 1 (each cycle is 21 days)

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: No statistical analysis for this end point.

End point values	Arm A (atezolizumab plus bevacizumab)			
Subject group type	Reporting group			
Number of subjects analysed	329			
Units: µg/ mL				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n=329)	999999 (± 999999)			
Cycle 1 Day 1, 30 Min After End of Atezo (n=310)	440 (± 132)			
Cycle 2 Day 1 (n=317)	88.7 (± 30.4)			
Cycle 3 Day 1 (n=314)	137 (± 53.0)			
Cycle 4 Day 1 (n=305)	159 (± 58.5)			
Cycle 8 Day 1 (n=264)	196 (± 86.2)			
Cycle 12 Day 1 (n=233)	202 (± 90.1)			
Cycle 16 Day 1 (n=192)	204 (± 89.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Anti-Drug Antibodies (ADAs) to Atezolizumab

End point title	Number of Participants with Anti-Drug Antibodies (ADAs) to Atezolizumab[20]

End point description:

Number of participants with anti-drug antibodies to atezolizumab.

End point type	Secondary

End point timeframe:

Prior to any drug administration up to approximately 33 month

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: No statistical analysis for this end point.

End point values	Arm A (atezolizumab plus bevacizumab)			
Subject group type	Reporting group			
Number of subjects analysed	328			
Units: Participants				
Baseline evaluable participants	8			
Post-baseline evaluable participants	75			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first study drug administration to the data cutoff date: 21 October 2022 (up to approximately 33 months).

Adverse event reporting additional description:

Adverse events reported based on safety population, which included participants who received any amount of any component of study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Arm A (Atezolizumab plus Bevacizumab)

Reporting group description:

Participants received Atezolizumab + Bevacizumab until disease recurrence or unacceptable toxicity.

Reporting group title	Arm B (Active Surveillance)

Reporting group description:

Active surveillance of participants.

Reporting group title	Crossover: Atezolizumab + Bevacizumab

Reporting group description:

Participants randomized to Active Surveillance arm who crossed over to receive treatment with Atezolizumab plus Bevacizumab during the Active Surveillance period or during the follow-up period.

Serious adverse events	Arm A (Atezolizumab plus Bevacizumab)	Arm B (Active Surveillance)	Crossover: Atezolizumab + Bevacizumab
Total subjects affected by serious adverse events			
subjects affected / exposed	80 / 332 (24.10%)	34 / 330 (10.30%)	10 / 81 (12.35%)
number of deaths (all causes)	28	19	11
number of deaths resulting from adverse events	2	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tonsillar neoplasm benign			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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
Prostate cancer			
subjects affected / exposed	0 / 332 (0.00%)	1 / 330 (0.30%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Papillary thyroid cancer			

subjects affected / exposed	0 / 332 (0.00%)	0 / 330 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine benign neoplasm			
subjects affected / exposed	0 / 332 (0.00%)	1 / 330 (0.30%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glioma			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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
Transitional cell carcinoma			
subjects affected / exposed	0 / 332 (0.00%)	1 / 330 (0.30%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric cancer			
subjects affected / exposed	0 / 332 (0.00%)	1 / 330 (0.30%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric adenoma			
subjects affected / exposed	0 / 332 (0.00%)	1 / 330 (0.30%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic myeloid leukaemia			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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
Bladder cancer			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric cancer stage 0			

subjects affected / exposed	0 / 332 (0.00%)	1 / 330 (0.30%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour necrosis			
subjects affected / exposed	0 / 332 (0.00%)	0 / 330 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic dissection			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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
Peripheral artery thrombosis			
subjects affected / exposed	0 / 332 (0.00%)	1 / 330 (0.30%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	3 / 332 (0.90%)	0 / 330 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	2 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Impaired healing			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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
Localised oedema			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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
Pyrexia			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	3 / 81 (3.70%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hernia			
subjects affected / exposed	0 / 332 (0.00%)	0 / 330 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 332 (0.00%)	1 / 330 (0.30%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 332 (0.00%)	1 / 330 (0.30%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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	3 / 332 (0.90%)	0 / 330 (0.00%)	0 / 81 (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
Pulmonary embolism			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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
Epistaxis			

subjects affected / exposed	2 / 332 (0.60%)	0 / 330 (0.00%)	0 / 81 (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
Hydrothorax			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 332 (0.00%)	1 / 330 (0.30%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 332 (0.00%)	1 / 330 (0.30%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Insomnia			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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
Anxiety			
subjects affected / exposed	0 / 332 (0.00%)	1 / 330 (0.30%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	0 / 332 (0.00%)	1 / 330 (0.30%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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
Transaminases increased			

subjects affected / exposed	0 / 332 (0.00%)	0 / 330 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	3 / 332 (0.90%)	0 / 330 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			
subjects affected / exposed	0 / 332 (0.00%)	1 / 330 (0.30%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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
Blood glucose increased			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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
Injury, poisoning and procedural complications			
Bone contusion			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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

Rib fracture			
subjects affected / exposed	2 / 332 (0.60%)	0 / 330 (0.00%)	0 / 81 (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
Craniocerebral injury			
subjects affected / exposed	0 / 332 (0.00%)	1 / 330 (0.30%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	0 / 332 (0.00%)	1 / 330 (0.30%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 332 (0.00%)	1 / 330 (0.30%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 332 (0.00%)	0 / 330 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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			
Epilepsy			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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

Cerebral infarction			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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
Cerebral haemorrhage			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic encephalopathy			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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
Transient ischaemic attack			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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
Myasthenia gravis			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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
Loss of consciousness			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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
Immune-mediated encephalitis			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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
Blood and lymphatic system disorders			

Thrombocytopenia			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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
Thrombotic microangiopathy			
subjects affected / exposed	0 / 332 (0.00%)	0 / 330 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 332 (0.00%)	0 / 330 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Deafness neurosensory			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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
Eye disorders			
Cataract			
subjects affected / exposed	0 / 332 (0.00%)	2 / 330 (0.61%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uveitis			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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
Retinal tear			
subjects affected / exposed	0 / 332 (0.00%)	1 / 330 (0.30%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal wall mass			

subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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
Abdominal pain upper			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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
Abdominal pain			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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
Abdominal hernia			
subjects affected / exposed	0 / 332 (0.00%)	1 / 330 (0.30%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 332 (0.60%)	1 / 330 (0.30%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal haemorrhage			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	3 / 332 (0.90%)	0 / 330 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	1 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	2 / 332 (0.60%)	0 / 330 (0.00%)	0 / 81 (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
Duodenal ulcer			

subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer haemorrhage			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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
Anal fistula			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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
Small intestinal perforation			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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
Proctitis			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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
Oesophageal varices haemorrhage			
subjects affected / exposed	5 / 332 (1.51%)	2 / 330 (0.61%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	5 / 6	0 / 2	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 1	0 / 0
Pancreatitis			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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
Pancreatitis acute			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine polyp			

subjects affected / exposed	1 / 332 (0.30%)	1 / 330 (0.30%)	0 / 81 (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
Intra-abdominal haematoma			
subjects affected / exposed	0 / 332 (0.00%)	1 / 330 (0.30%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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
Inguinal hernia			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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
Incarcerated inguinal hernia			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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
Haemorrhoids			
subjects affected / exposed	0 / 332 (0.00%)	0 / 330 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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
Varices oesophageal			
subjects affected / exposed	2 / 332 (0.60%)	0 / 330 (0.00%)	0 / 81 (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
Hepatobiliary disorders			
Acute hepatic failure			

subjects affected / exposed	2 / 332 (0.60%)	0 / 330 (0.00%)	0 / 81 (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
Bile duct stone			
subjects affected / exposed	0 / 332 (0.00%)	3 / 330 (0.91%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bile duct stenosis			
subjects affected / exposed	0 / 332 (0.00%)	1 / 330 (0.30%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Portal vein thrombosis			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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
Jaundice			
subjects affected / exposed	0 / 332 (0.00%)	1 / 330 (0.30%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune-mediated hepatitis			
subjects affected / exposed	2 / 332 (0.60%)	0 / 330 (0.00%)	0 / 81 (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
Cholangitis			
subjects affected / exposed	0 / 332 (0.00%)	1 / 330 (0.30%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis acute			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			

subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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 function abnormal			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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
Cholelithiasis			
subjects affected / exposed	0 / 332 (0.00%)	1 / 330 (0.30%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Pyoderma gangrenosum			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract obstruction			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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
Tubulointerstitial nephritis			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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 impairment			

subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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
Calculus bladder			
subjects affected / exposed	0 / 332 (0.00%)	1 / 330 (0.30%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic kidney disease			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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
Nephrotic syndrome			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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
Hypopituitarism			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			

Foot deformity			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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
Intervertebral disc protrusion			
subjects affected / exposed	1 / 332 (0.30%)	1 / 330 (0.30%)	0 / 81 (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
Osteoarthritis			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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
Anal abscess			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	4 / 332 (1.20%)	0 / 330 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
COVID-19 pneumonia			
subjects affected / exposed	0 / 332 (0.00%)	1 / 330 (0.30%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Implant site infection			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious pleural effusion			

subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver abscess			
subjects affected / exposed	1 / 332 (0.30%)	1 / 330 (0.30%)	0 / 81 (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
Meningitis bacterial			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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
Otitis media			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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
Periodontitis			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	2 / 332 (0.60%)	1 / 330 (0.30%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Post procedural sepsis			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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 / 332 (0.30%)	0 / 330 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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
Metabolism and nutrition disorders			
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 332 (0.30%)	0 / 330 (0.00%)	0 / 81 (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

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

Non-serious adverse events	Arm A (Atezolizumab plus Bevacizumab)	Arm B (Active Surveillance)	Crossover: Atezolizumab + Bevacizumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	296 / 332 (89.16%)	111 / 330 (33.64%)	63 / 81 (77.78%)
Vascular disorders			
Hypertension			
subjects affected / exposed	126 / 332 (37.95%)	10 / 330 (3.03%)	25 / 81 (30.86%)
occurrences (all)	157	11	28
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	28 / 332 (8.43%)	4 / 330 (1.21%)	5 / 81 (6.17%)
occurrences (all)	31	4	5
Pyrexia			
subjects affected / exposed	33 / 332 (9.94%)	7 / 330 (2.12%)	6 / 81 (7.41%)
occurrences (all)	41	7	7
Oedema peripheral			

subjects affected / exposed	18 / 332 (5.42%)	2 / 330 (0.61%)	1 / 81 (1.23%)
occurrences (all)	20	2	3
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	22 / 332 (6.63%)	7 / 330 (2.12%)	1 / 81 (1.23%)
occurrences (all)	22	7	1
Epistaxis			
subjects affected / exposed	20 / 332 (6.02%)	1 / 330 (0.30%)	6 / 81 (7.41%)
occurrences (all)	23	1	6
Investigations			
Blood bilirubin increased			
subjects affected / exposed	33 / 332 (9.94%)	23 / 330 (6.97%)	7 / 81 (8.64%)
occurrences (all)	59	30	8
Gamma-glutamyltransferase increased			
subjects affected / exposed	17 / 332 (5.12%)	5 / 330 (1.52%)	3 / 81 (3.70%)
occurrences (all)	26	5	4
Lymphocyte count decreased			
subjects affected / exposed	22 / 332 (6.63%)	6 / 330 (1.82%)	2 / 81 (2.47%)
occurrences (all)	37	7	3
Aspartate aminotransferase increased			
subjects affected / exposed	51 / 332 (15.36%)	18 / 330 (5.45%)	13 / 81 (16.05%)
occurrences (all)	67	18	16
Alanine aminotransferase increased			
subjects affected / exposed	46 / 332 (13.86%)	18 / 330 (5.45%)	12 / 81 (14.81%)
occurrences (all)	58	19	16
Neutrophil count decreased			
subjects affected / exposed	29 / 332 (8.73%)	8 / 330 (2.42%)	5 / 81 (6.17%)
occurrences (all)	60	12	5
Platelet count decreased			
subjects affected / exposed	66 / 332 (19.88%)	22 / 330 (6.67%)	17 / 81 (20.99%)
occurrences (all)	101	27	19
Weight increased			
subjects affected / exposed	17 / 332 (5.12%)	11 / 330 (3.33%)	0 / 81 (0.00%)
occurrences (all)	26	12	0
White blood cell count decreased			

subjects affected / exposed	28 / 332 (8.43%)	10 / 330 (3.03%)	3 / 81 (3.70%)
occurrences (all)	76	13	4
Nervous system disorders			
Headache			
subjects affected / exposed	19 / 332 (5.72%)	6 / 330 (1.82%)	2 / 81 (2.47%)
occurrences (all)	23	6	3
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	12 / 332 (3.61%)	4 / 330 (1.21%)	5 / 81 (6.17%)
occurrences (all)	12	4	8
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	29 / 332 (8.73%)	10 / 330 (3.03%)	4 / 81 (4.94%)
occurrences (all)	38	11	4
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	40 / 332 (12.05%)	3 / 330 (0.91%)	6 / 81 (7.41%)
occurrences (all)	45	3	7
Rash			
subjects affected / exposed	40 / 332 (12.05%)	1 / 330 (0.30%)	9 / 81 (11.11%)
occurrences (all)	44	1	9
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	21 / 332 (6.33%)	2 / 330 (0.61%)	3 / 81 (3.70%)
occurrences (all)	34	2	3
Proteinuria			
subjects affected / exposed	153 / 332 (46.08%)	12 / 330 (3.64%)	25 / 81 (30.86%)
occurrences (all)	227	14	29
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	47 / 332 (14.16%)	1 / 330 (0.30%)	9 / 81 (11.11%)
occurrences (all)	49	1	9
Hyperthyroidism			
subjects affected / exposed	21 / 332 (6.33%)	0 / 330 (0.00%)	4 / 81 (4.94%)
occurrences (all)	21	0	5
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	40 / 332 (12.05%)	8 / 330 (2.42%)	8 / 81 (9.88%)
occurrences (all)	43	9	9
Myalgia			
subjects affected / exposed	32 / 332 (9.64%)	1 / 330 (0.30%)	1 / 81 (1.23%)
occurrences (all)	39	1	1
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	25 / 332 (7.53%)	9 / 330 (2.73%)	1 / 81 (1.23%)
occurrences (all)	27	11	1
Metabolism and nutrition disorders			
Hypoalbuminaemia			
subjects affected / exposed	21 / 332 (6.33%)	2 / 330 (0.61%)	0 / 81 (0.00%)
occurrences (all)	32	2	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 December 2019	Protocol was amended to include combining three of the previous stratification factors and restructured to combine high-risk features, curative procedures, and adjuvant TACE into one stratification factor with 5 strata. IRF and investigator-assessed RFS rate at 24 and 36 months after randomization was added as a secondary endpoint. An exclusion criterion was added to clarify that participants who have more than one treatment with TACE were excluded from the study. The list of atezolizumab risks was updated to include myositis. SIA was replaced by HLH and MAS in the list of potential risks for atezolizumab and the management guidelines for SIA were replaced with management guidelines for HLH and MAS.
03 December 2020	Protocol was amended to include treatment language to allow participants to receive up to 17 cycles of treatment even if this extended beyond 12 months. Exclusion criteria was amended with co-infection with HBV and hepatitis D virus was not allowed. Language in exclusion criteria was updated regarding use of anticoagulants to address the risk of upper gastrointestinal bleeding in patients with HCC. Lists of identified risks for atezolizumab was revised to include severe cutaneous adverse reactions. All identified risks related to bevacizumab was added.
30 November 2021	Protocol was amended to include language to indicate that bevacizumab should be held in the event that atezolizumab was held for an Adverse Event during both the treatment period and the crossover period. Details of the OS analyses including the estimated number of events expected at the interim and final analyses and the efficacy boundaries that will be used have been added for completeness.
25 October 2022	Protocol has been amended to include pericardial disorders in the list of identified risks for atezolizumab.
23 March 2023	Protocol has been amended to include revision to the list of identified risks for atezolizumab to include myelitis and facial paresis. Hemophagocytic lymphohistiocytosis has been updated from a potential risk to an identified risk associated with atezolizumab and language has been revised accordingly.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported