Clinical trial results:
A Phase IIIB, Single Arm, Multicenter Study of Atezolizumab (Tecentriq) in Combination With Bevacizumab to Investigate Safety and Efficacy in Patients With Unresectable Hepatocellular Carcinoma Not Previously Treated With Systemic Therapy-AMETHISTA

Summary

EudraCT number	2020-001973-66
Trial protocol	IT
Global end of trial date	13 August 2024

Results information

Result version number	v1
This version publication date	27 August 2025
First version publication date	27 August 2025

Trial information

Trial identification

Sponsor protocol code	ML42243

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04487067
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4058
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	26 May 2025
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 August 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary purpose of this study was to evaluate the safety of atezolizumab in combination with bevacizumab in terms of bleeding/haemorrhage in participants with unresectable hepatocellular carcinoma (HCC) who received no prior systemic treatment.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 August 2020
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	44 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 152
Worldwide total number of subjects	152
EEA total number of subjects	152

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)	60
From 65 to 84 years	87
85 years and over	5

Subject disposition

Recruitment

Recruitment details:

A total of 152 participants with unresectable HCC and no prior systemic treatment took part in the study at 21 investigative sites in Italy from 25 August 2020 to 13 August 2024.

Pre-assignment

Screening details:

Participants received atezolizumab in combination with bevacizumab until unacceptable toxicity or loss of clinical benefit as determined by the investigator. Of the 152 participants enrolled, three participants did not receive any treatment.

Period 1

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

Arms

Arm title	Atezolizumab + Bevacizumab

Arm description:

Participants received atezolizumab, 1200 milligrams (mg) as intravenous (IV) infusion, along with bevacizumab, 15 milligrams/kilogram (mg/kg), also as IV infusion, every 3 weeks (Q3W) on Day 1 of each 21-day cycle 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	RO4876646
Other name	Avastin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab, 15 mg/kg, IV, was administered Q3W on Day 1 of each 21-day cycle.

Investigational medicinal product name	Atezolizumab
Investigational medicinal product code	RO5541267
Other name	Tecentriq
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Atezolizumab, 1200 mg, IV, was administered Q3W on Day 1 of each 21-day cycle.

Number of subjects in period 1	Atezolizumab + Bevacizumab
Started	152
Safety analysis population	149
Completed	21
Not completed	131
Consent withdrawn by subject	15
Adverse Event	3

Progressive Disease	1
Discontinuation From Study as per Protocol	6
Death Due To Progressive Disease	40
Lost to follow-up	3
Death Other Than Progressive Disease	60
Protocol deviation	3

Baseline characteristics

Reporting groups	
Reporting group title	Atezolizumab + Bevacizumab
Reporting group description:	
Participants received atezolizumab, 1200 milligrams (mg) as intravenous (IV) infusion, along with bevacizumab, 15 milligrams/kilogram (mg/kg), also as IV infusion, every 3 weeks (Q3W) on Day 1 of each 21-day cycle until unacceptable toxicity or loss of clinical benefit as determined by the investigator.	

Reporting group values	Atezolizumab + Bevacizumab	Total	
Number of subjects	152	152	
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	67.1		
standard deviation	± 10.52	-	
Sex: Female, Male Units: participants			
Female	31	31	
Male	121	121	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	3	3	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	145	145	
More than one race	0	0	
Unknown or Not Reported	4	4	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	5	5	
Not Hispanic or Latino	141	141	
Unknown or Not Reported	6	6	

End points

End points reporting groups

Reporting group title	Atezolizumab + Bevacizumab

Reporting group description:

Participants received atezolizumab, 1200 milligrams (mg) as intravenous (IV) infusion, along with bevacizumab, 15 milligrams/kilogram (mg/kg), also as IV infusion, every 3 weeks (Q3W) on Day 1 of each 21-day cycle until unacceptable toxicity or loss of clinical benefit as determined by the investigator.

Primary: Number of Participants With Grade 3-5 National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0) Bleeding/Haemorrhage

End point title	Number of Participants With Grade 3-5 National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0) Bleeding/Haemorrhage[1]

End point description:

An adverse event (AE) was any untoward medical occurrence in a clinical investigation participant administered a pharmaceutical product, regardless of causal attribution. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Severity of AEs was graded using NCI CTCAE v5.0. Grade 3=Severe/medically significant but not immediately life-threatening, hospitalization/prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living; Grade 4=Life-threatening consequences, urgent intervention indicated; Grade 5=Death related to AE. Safety analysis population included all enrolled participants who had at least one full or partial administration of atezolizumab plus bevacizumab.

End point type	Primary

End point timeframe:

Up to approximately 47.6 months

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis for the end point.

End point values	Atezolizumab + Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	149			
Units: participants				
Grade 3	17			
Grade 4	3			
Grade 5	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

ORR was defined as the percentage of participants with complete or partial response (CR or PR), as

determined by the investigator according to RECIST v1.1. CR was defined as disappearance of all target lesions or any pathological lymph nodes must have reduction in short axis to < 10 mm. PR was defined as at least a 30% decrease in the SOD of all target lesions, taking as reference the baseline SOD, in the absence of CR. ITT population included all participants who signed the ICF and were enrolled in the study.

End point type	Secondary

End point timeframe:

Up to approximately 47.6 months

End point values	Atezolizumab + Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	152			
Units: percentage of participants				
number (not applicable)	28.29			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)

End point description:

PFS was defined as the time from initiation of study treatment to the first occurrence of disease progression (PD) or death from any cause (whichever occurs first), as determined by the investigator according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1). PD was defined as at least a 20% increase in the sum of diameters (SOD) of target lesions, taking as reference the smallest SOD at prior timepoints (including baseline). In addition to the relative increase of 20%, the SOD must also demonstrate an absolute increase of ≥ 5 millimeters (mm). Participants alive and without any PD were censored at the last assessment date. K-M method was used to estimate the PFS. ITT population included all participants who signed the ICF and were enrolled in the study. Number analyzed is the number of participants with data available for analysis.

End point type	Secondary

End point timeframe:

Up to approximately 47.6 months

End point values	Atezolizumab + Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	149			
Units: months				
median (confidence interval 95%)	8.80 (7.89 to 11.24)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression (TTP)

End point title	Time to Progression (TTP)

End point description:

TTP was defined as the time from initiation of study treatment to the first occurrence of PD, as determined by the investigator according to RECIST v1.1. PD was defined as at least a 20% increase in the SOD of target lesions, taking as reference the smallest SOD at prior timepoints (including baseline). In addition to the relative increase of 20%, the SOD must also demonstrate an absolute increase of ≥ 5 mm. Participants without any PD were censored at the last assessment date. K-M method was used to estimate the TTP. ITT population included all participants who signed the ICF and were enrolled in the study. Number analyzed is the number of participants with data available for analysis.

End point type	Secondary

End point timeframe:

Up to approximately 47.6 months

End point values	Atezolizumab + Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	149			
Units: months				
median (confidence interval 95%)	11.24 (8.48 to 15.77)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-Emergent Adverse Events (TEAEs)

End point title	Number of Participants With Treatment-Emergent Adverse Events (TEAEs)

End point description:

An AE was any untoward medical occurrence in a clinical investigation participant administered a pharmaceutical product, regardless of causal attribution. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. TEAEs are defined as AEs with onset date on or after the start of the first study treatment component. Safety analysis population included all enrolled participants who had at least one full or partial administration of atezolizumab plus bevacizumab. Number of participants with any TEAEs are reported here.

End point type	Secondary

End point timeframe:

Up to approximately 47.6 months

End point values	Atezolizumab + Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	149			
Units: participants	144			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from initiation of study treatment to death from any cause. Kaplan-Meier (K-M) method was used to estimate the OS. ITT population included all participants who signed the ICF and were enrolled in the study. Number analyzed is the number of participants with data available for analysis.

End point type	Secondary

End point timeframe:

Up to approximately 47.6 months

End point values	Atezolizumab + Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	149			
Units: months				
median (confidence interval 95%)	20.76 (16.85 to 26.35)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Reporting Severe Symptoms in Patient-Reported Outcomes of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) Questionnaire

End point title	Number of Participants Reporting Severe Symptoms in Patient-Reported Outcomes of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) Questionnaire

End point description:

Participants self-reported symptomatic AEs using PRO-CTCAE, a validated item bank used to characterize presence, frequency of occurrence, severity, &/or degree of interference with daily function of 78 patient-reportable symptomatic treatment toxicities. PRO-CTCAE contains questions that are rated either dichotomously (for determination of presence vs. absence)/ on a 5-point Likert scale (for determination of frequency of occurrence,severity,& interference with daily function). Treatment toxicities can occur with observable signs (e.g.,vomiting)/ non-observable symptoms (e.g.,nausea). Subset of 14 symptoms most applicable to current treatments were selected for this study. Symptoms were selected based on toxicities associated with drug's class, mechanism of action, or mode of administration, & toxicities reported with drug in another indication. Participants reporting severe

symptoms per the PRO-CTCAE questionnaire on Day 1 of each cycle is reported here. Safety analysis population.

End point type	Secondary

End point timeframe:

From Cycle 1 Day 1 to Cycle 63 Day 1 (1 Cycle = 21 days)

End point values	Atezolizumab + Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	149			
Units: participants				
Cycle 1 Day 1	39			
Cycle 2 Day 1	33			
Cycle 3 Day 1	23			
Cycle 4 Day 1	30			
Cycle 5 Day 1	23			
Cycle 6 Day 1	22			
Cycle 7 Day 1	17			
Cycle 8 Day 1	14			
Cycle 9 Day 1	19			
Cycle 10 Day 1	16			
Cycle 11 Day 1	17			
Cycle 12 Day 1	16			
Cycle 13 Day 1	13			
Cycle 14 Day 1	13			
Cycle 15 Day 1	9			
Cycle 16 Day 1	8			
Cycle 17 Day 1	10			
Cycle 18 Day 1	10			
Cycle 19 Day 1	8			
Cycle 20 Day 1	11			
Cycle 21 Day 1	5			
Cycle 22 Day 1	6			
Cycle 23 Day 1	8			
Cycle 24 Day 1	10			
Cycle 25 Day 1	8			
Cycle 26 Day 1	7			
Cycle 27 Day 1	8			
Cycle 28 Day 1	10			
Cycle 29 Day 1	6			
Cycle 30 Day 1	7			
Cycle 31 Day 1	7			
Cycle 32 Day 1	6			
Cycle 33 Day 1	6			
Cycle 34 Day 1	7			
Cycle 35 Day 1	9			
Cycle 36 Day 1	8			
Cycle 37 Day 1	7			
Cycle 38 Day 1	9			

Cycle 39 Day 1	8			
Cycle 40 Day 1	8			
Cycle 41 Day 1	5			
Cycle 42 Day 1	6			
Cycle 43 Day 1	3			
Cycle 44 Day 1	3			
Cycle 45 Day 1	3			
Cycle 46 Day 1	2			
Cycle 47 Day 1	2			
Cycle 48 Day 1	3			
Cycle 49 Day 1	3			
Cycle 50 Day 1	2			
Cycle 51 Day 1	3			
Cycle 52 Day 1	2			
Cycle 53 Day 1	2			
Cycle 54 Day 1	1			
Cycle 55 Day 1	1			
Cycle 56 Day 1	1			
Cycle 57 Day 1	0			
Cycle 58 Day 1	0			
Cycle 59 Day 1	0			
Cycle 60 Day 1	0			
Cycle 61 Day 1	0			
Cycle 62 Day 1	0			
Cycle 63 Day 1	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

DOR was defined as the time from the first occurrence of a documented objective response (CR or PR) to PD or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1. CR=disappearance of all target lesions or any pathological lymph nodes must have reduction in short axis to < 10 mm. PR=at least a 30% decrease in the SOD of all target lesions, taking as reference the baseline SOD, in the absence of CR. PD was defined as at least a 20% increase in the SOD of target lesions, taking as reference the smallest SOD at prior timepoints (including baseline). In addition to the relative increase of 20%, the SOD must also demonstrate an absolute increase of ≥ 5 mm. Participants who were alive and without any PD were censored at the last assessment date. K-M method was used to estimate the DOR. ITT population included all participants who signed the ICF and were enrolled in the study. Number analyzed is the number of participants with CR or PR.

End point type	Secondary

End point timeframe:

Up to approximately 47.6 months

End point values	Atezolizumab + Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: months				
median (confidence interval 95%)	17.35 (13.54 to 27.24)			

Statistical analyses

No statistical analyses for this end point

Secondary: Post-progression Survival (PPS)

End point title	Post-progression Survival (PPS)

End point description:

PPS was defined as the time from the first occurrence of PD as determined by the investigator according to RECIST v1.1 to death from any cause. PD was defined as at least a 20% increase in the SOD of target lesions, taking as reference the smallest SOD at prior timepoints (including baseline). In addition to the relative increase of 20%, the SOD must also demonstrate an absolute increase of ≥ 5 mm. Participants who were alive were censored at the last assessment date. K-M method was used to estimate the PPS. ITT population included all participants who signed the ICF and were enrolled in the study. Number analyzed is the number of participants with a progressive disease.

End point type	Secondary

End point timeframe:

Up to approximately 47.6 months

End point values	Atezolizumab + Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	97			
Units: months				
median (confidence interval 95%)	11.27 (8.41 to 13.80)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Reporting Very Severe Symptoms in PRO-CTCAE Questionnaire

End point title	Number of Participants Reporting Very Severe Symptoms in PRO-CTCAE Questionnaire

End point description:

Participants self-reported symptomatic AEs using PRO-CTCAE, a validated item bank used to characterize presence, frequency of occurrence, severity, &/or degree of interference with daily function of 78 patient-reportable symptomatic treatment toxicities. PRO-CTCAE contains questions that are rated either dichotomously (for determination of presence vs. absence)/ on a 5-point Likert scale (for determination of frequency of occurrence,severity & interference with daily function). Treatment toxicities can occur with observable signs (e.g.vomiting)/ non-observable symptoms (e.g.nausea).

Subset of 14 symptoms most applicable to current treatments were selected for this study. Symptoms were selected based on toxicities associated with drug's class, mechanism of action/ mode of administration, & toxicities reported with drug in another indication. Participants reporting very severe symptoms per the PRO-CTCAE questionnaire on Day 1 of each cycle is reported here. Safety analysis population.

End point type	Secondary

End point timeframe:

From Cycle 1 Day 1 to Cycle 63 Day 1 (1 Cycle = 21 days)

End point values	Atezolizumab + Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	149			
Units: participants				
Cycle 1 Day 1	15			
Cycle 2 Day 1	18			
Cycle 3 Day 1	12			
Cycle 4 Day 1	12			
Cycle 5 Day 1	10			
Cycle 6 Day 1	11			
Cycle 7 Day 1	7			
Cycle 8 Day 1	11			
Cycle 9 Day 1	7			
Cycle 10 Day 1	7			
Cycle 11 Day 1	6			
Cycle 12 Day 1	5			
Cycle 13 Day 1	7			
Cycle 14 Day 1	7			
Cycle 15 Day 1	7			
Cycle 16 Day 1	8			
Cycle 17 Day 1	4			
Cycle 18 Day 1	5			
Cycle 19 Day 1	4			
Cycle 20 Day 1	4			
Cycle 21 Day 1	1			
Cycle 22 Day 1	4			
Cycle 23 Day 1	2			
Cycle 24 Day 1	3			
Cycle 25 Day 1	4			
Cycle 26 Day 1	4			
Cycle 27 Day 1	3			
Cycle 28 Day 1	3			
Cycle 29 Day 1	3			
Cycle 30 Day 1	2			
Cycle 31 Day 1	4			
Cycle 32 Day 1	3			
Cycle 33 Day 1	3			
Cycle 34 Day 1	5			
Cycle 35 Day 1	5			
Cycle 36 Day 1	3			

Cycle 37 Day 1	6			
Cycle 38 Day 1	4			
Cycle 39 Day 1	4			
Cycle 40 Day 1	4			
Cycle 41 Day 1	4			
Cycle 42 Day 1	5			
Cycle 43 Day 1	4			
Cycle 44 Day 1	4			
Cycle 45 Day 1	2			
Cycle 46 Day 1	2			
Cycle 47 Day 1	1			
Cycle 48 Day 1	1			
Cycle 49 Day 1	0			
Cycle 50 Day 1	1			
Cycle 51 Day 1	0			
Cycle 52 Day 1	1			
Cycle 53 Day 1	1			
Cycle 54 Day 1	0			
Cycle 55 Day 1	1			
Cycle 56 Day 1	0			
Cycle 57 Day 1	1			
Cycle 58 Day 1	0			
Cycle 59 Day 1	0			
Cycle 60 Day 1	0			
Cycle 61 Day 1	0			
Cycle 62 Day 1	0			
Cycle 63 Day 1	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Other AEs: Up to approximately 44 months
SAEs and All-cause Mortality: Up to approximately 47.6 months

Adverse event reporting additional description:

Safety analysis population included all enrolled participants who had at least one full or partial administration of atezolizumab plus bevacizumab.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.1

Reporting groups

Reporting group title	Atezolizumab + Bevacizumab

Reporting group description:

Participants received atezolizumab, 1200 mg as IV infusion, along with bevacizumab, 15 mg/kg, also as IV infusion, Q3W on Day 1 of each 21-day cycle until unacceptable toxicity or loss of clinical benefit as determined by the investigator.

Serious adverse events	Atezolizumab + Bevacizumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	62 / 149 (41.61%)		
number of deaths (all causes)	102		
number of deaths resulting from adverse events	3		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour haemorrhage			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Haemorrhage			
subjects affected / exposed	2 / 149 (1.34%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Deep vein thrombosis			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pelvic venous thrombosis			

subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Shock haemorrhagic			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Thrombophlebitis			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Leg amputation			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Oedema			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Oedema peripheral			
subjects affected / exposed	2 / 149 (1.34%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	2 / 149 (1.34%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Epistaxis			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Haemoptysis			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Interstitial lung disease			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	5 / 149 (3.36%)		
occurrences causally related to treatment / all	4 / 5		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Electrocardiogram abnormal			

subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Accidental exposure to product			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Femur fracture			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Humerus fracture			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infusion related reaction			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thermal burn			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ulna fracture			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wound dehiscence			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			

Cardiac arrest				
subjects affected / exposed	1 / 149 (0.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cardiac failure				
subjects affected / exposed	1 / 149 (0.67%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	1 / 149 (0.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Bradycardia				
subjects affected / exposed	1 / 149 (0.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Angina unstable				
subjects affected / exposed	1 / 149 (0.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Ataxia				
subjects affected / exposed	1 / 149 (0.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Encephalopathy				
subjects affected / exposed	2 / 149 (1.34%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	2 / 149 (1.34%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Hepatic encephalopathy				

subjects affected / exposed	2 / 149 (1.34%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemic coma			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	2 / 149 (1.34%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anaemia			
subjects affected / exposed	3 / 149 (2.01%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Diplopia			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Enterovesical fistula				
subjects affected / exposed	1 / 149 (0.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Gastric haemorrhage				
subjects affected / exposed	1 / 149 (0.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	3 / 149 (2.01%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Haematemesis				
subjects affected / exposed	1 / 149 (0.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Haemoperitoneum				
subjects affected / exposed	1 / 149 (0.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Large intestinal haemorrhage				
subjects affected / exposed	1 / 149 (0.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Melaena				
subjects affected / exposed	2 / 149 (1.34%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Ascites				
subjects affected / exposed	3 / 149 (2.01%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 1			
Oesophageal varices haemorrhage				

subjects affected / exposed	4 / 149 (2.68%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Pancreatic haemorrhage				
subjects affected / exposed	1 / 149 (0.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage				
subjects affected / exposed	1 / 149 (0.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Small intestinal haemorrhage				
subjects affected / exposed	1 / 149 (0.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Upper gastrointestinal haemorrhage				
subjects affected / exposed	2 / 149 (1.34%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Bile duct stone				
subjects affected / exposed	1 / 149 (0.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholangitis				
subjects affected / exposed	1 / 149 (0.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholecystitis				
subjects affected / exposed	1 / 149 (0.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic failure				

subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Skin and subcutaneous tissue disorders			
Dermatitis bullous			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Purpura			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Proteinuria			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Infections and infestations			
Biliary tract infection			
subjects affected / exposed	2 / 149 (1.34%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Brain abscess			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

COVID-19			
subjects affected / exposed	4 / 149 (2.68%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 1		
COVID-19 pneumonia			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Gangrene			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peri-implantitis			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	2 / 149 (1.34%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Sepsis			
subjects affected / exposed	5 / 149 (3.36%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 1		
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 149 (0.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Atezolizumab + Bevacizumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	142 / 149 (95.30%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	51 / 149 (34.23%)		
occurrences (all)	99		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	64 / 149 (42.95%)		
occurrences (all)	97		
Fatigue			
subjects affected / exposed	26 / 149 (17.45%)		
occurrences (all)	30		
Oedema peripheral			
subjects affected / exposed	12 / 149 (8.05%)		
occurrences (all)	14		
Mucosal inflammation			
subjects affected / exposed	10 / 149 (6.71%)		
occurrences (all)	12		
Pyrexia			
subjects affected / exposed	32 / 149 (21.48%)		
occurrences (all)	38		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	21 / 149 (14.09%)		
occurrences (all)	29		
Epistaxis			
subjects affected / exposed	18 / 149 (12.08%)		
occurrences (all)	23		
Dysphonia			
subjects affected / exposed	9 / 149 (6.04%)		
occurrences (all)	9		

Dyspnoea subjects affected / exposed occurrences (all)	8 / 149 (5.37%) 8		
Investigations Blood bilirubin increased subjects affected / exposed occurrences (all) Platelet count decreased subjects affected / exposed occurrences (all) Aspartate aminotransferase increased subjects affected / exposed occurrences (all) Alanine aminotransferase increased subjects affected / exposed occurrences (all)	 13 / 149 (8.72%) 21 11 / 149 (7.38%) 19 11 / 149 (7.38%) 14 8 / 149 (5.37%) 10		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	 18 / 149 (12.08%) 21		
Blood and lymphatic system disorders Thrombocytopenia subjects affected / exposed occurrences (all) Anaemia subjects affected / exposed occurrences (all)	 16 / 149 (10.74%) 35 15 / 149 (10.07%) 17		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Nausea	 42 / 149 (28.19%) 64 25 / 149 (16.78%) 32		

subjects affected / exposed occurrences (all)	22 / 149 (14.77%) 28		
Ascites subjects affected / exposed occurrences (all)	16 / 149 (10.74%) 18		
Abdominal pain upper subjects affected / exposed occurrences (all)	14 / 149 (9.40%) 16		
Constipation subjects affected / exposed occurrences (all)	14 / 149 (9.40%) 16		
Vomiting subjects affected / exposed occurrences (all)	14 / 149 (9.40%) 15		
Stomatitis subjects affected / exposed occurrences (all)	10 / 149 (6.71%) 10		
Hepatobiliary disorders Hypertransaminasaemia subjects affected / exposed occurrences (all)	9 / 149 (6.04%) 13		
Hyperbilirubinaemia subjects affected / exposed occurrences (all)	8 / 149 (5.37%) 11		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	36 / 149 (24.16%) 46		
Renal and urinary disorders Proteinuria subjects affected / exposed occurrences (all)	28 / 149 (18.79%) 48		
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	17 / 149 (11.41%) 20		
Musculoskeletal and connective tissue			

disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all)	 24 / 149 (16.11%) 43 15 / 149 (10.07%) 16		
Infections and infestations COVID-19 subjects affected / exposed occurrences (all)	 13 / 149 (8.72%) 14		
Metabolism and nutrition disorders Decreased Appetite subjects affected / exposed occurrences (all)	 33 / 149 (22.15%) 42		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 March 2021	The following changes were made as per amendment 1: The number of sites were updated to comply with the actual number of investigational sites (21); The inclusion criterion on contraception was modified for better clarity; The option of 'any severe infection that in the opinion of the investigator could impact participant's safety' was added to the list of types of infections that require the exclusion of the participant from the study; Co-infection with hepatitis B virus (HBV) and hepatitis D viral infection was added as an exclusion criterion; Further specifications on exclusion due to anticoagulants or thrombolytic agents were added for better clarity.
13 December 2021	The following changes were made as per amendment 2: The second interim analysis, which was planned; A specification that live, attenuated vaccines are not permitted was added for better clarity; Specification on evaluation of post-progression tumor changes and on use of radiopharmaceutical products was added for better clarity; The RECIST v1.1 criteria for overall response at a single time point was modified to reflect the latest updated RECIST criteria.
11 January 2022	The following changes were made as per amendment 3: A specification on childbearing potential was added for better clarity; Specification on evaluation of post-progression tumor changes and on use of radiopharmaceutical products was added for better clarity.
15 February 2023	The following changes was made as per amendment 4: The list of identified risks for atezolizumab was revised to include pericardial disorders, facial paresis, and myelitis; The AE management guidelines had been updated to align with the Atezolizumab Investigator's Brochure, Version 19 and the Atezolizumab Investigator's Brochure Version 19, Addendum 1 and 2.
11 January 2024	The following change was made as per amendment 5: The Risks Associated with Atezolizumab and Guidelines for Management of AEs Associated with Atezolizumab was updated to align with the Atezolizumab Investigator's Brochure, Version 20.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported