Clinical trial results:
A Phase IIIB, Single arm, Multicenter Study of Atezolizumab in Combination With Bevacizumab to Investigate Safety and Efficacy in Spanish Patients With Unresectable or Unsuitable for Locoregional Treatments Hepatocellular Carcinoma not Previously Treated With Systemic Therapy

Summary

EudraCT number	2020-005268-71
Trial protocol	ES
Global end of trial date	26 April 2024

Results information

Result version number	v1 (current)
This version publication date	08 May 2025
First version publication date	08 May 2025

Trial information

Trial identification

Sponsor protocol code	ML42600

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04732286
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 April 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 April 2024
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main purpose of the study was to evaluate the safety of atezolizumab in combination with bevacizumab in participants with unresectable hepatocellular carcinoma (HCC) who have received no prior systemic treatment and are considered unsuitable for locoregional therapy.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 May 2021
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	35 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 100
Worldwide total number of subjects	100
EEA total number of subjects	100

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)	45
From 65 to 84 years	54
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

A total of 100 participants took part in the study in Spain from 04 May 2021 to 26 April 2024.

Pre-assignment

Screening details:

Participants with unresectable HCC who received no prior systemic treatment and were considered unsuitable for locoregional therapy were enrolled in this study to receive a combination of atezolizumab plus bevacizumab until unacceptable toxicity or loss of clinical benefit.

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), intravenously (IV), every 3 weeks (Q3W) along with bevacizumab, 15 milligrams per kilogram (mg/kg), IV, Q3W on Day 1 of each 21-day cycle until unacceptable toxicity or loss of clinical benefit.

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	100
Intent-to-treat population (ITT)	99
Completed	0
Not completed	100
Physician decision	1
Consent withdrawn by subject	10
Non-compliance With Study Drug	1

Death	51
Progressive Disease	2
Study Terminated by Sponsor	31
Lost to follow-up	4

Baseline characteristics

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

Reporting group values	Atezolizumab + Bevacizumab	Total	
Number of subjects	100	100	
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	65.4		
standard deviation	± 8.2	-	
Sex: Female, Male Units: participants			
Female	13	13	
Male	87	87	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	1	1	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	99	99	
More than one race	0	0	
Unknown or Not Reported	0	0	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	27	27	
Not Hispanic or Latino	73	73	
Unknown or Not Reported	0	0	

End points

End points reporting groups

Reporting group title	Atezolizumab + Bevacizumab

Reporting group description:

Participants received atezolizumab, 1200 milligrams (mg), intravenously (IV), every 3 weeks (Q3W) along with bevacizumab, 15 milligrams per kilogram (mg/kg), IV, Q3W on Day 1 of each 21-day cycle until unacceptable toxicity or loss of clinical benefit.

Primary: Number of Participants Who Discontinued Atezolizumab and/or Bevacizumab Due to Adverse Events (AE) of Grade ≥ 3

End point title	Number of Participants Who Discontinued Atezolizumab and/or Bevacizumab Due to Adverse Events (AE) of Grade ≥ 3[1]

End point description:

AE is any untoward medical occurrence in a clinical investigation participant administered a pharmaceutical product, regardless of causal attribution. An AE can be any unfavourable & 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. The severity of AEs was assessed using National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI CTCAE v5.0) with the following grades: Grade 1 = asymptomatic or mild symptoms; Grade 2 = minimal, local, or non-invasive intervention indicated; Grade 3 = severe or medically significant, but not immediately life-threatening; Grade 4 = life-threatening consequences or urgent intervention indicated and Grade 5 = death related to AE. Safety population= all screened participants (participants who signed the ICF) who received at least one full or partial dose of study treatment.

End point type	Primary

End point timeframe:

From Cycle 1 Day 1 up to 30 days after the final dose of the study drug or until initiation of another anti-cancer therapy, whichever occurred first (up to approximately 32 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 formal statistical analysis was planned for this outcome measure.

End point values	Atezolizumab + Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	100			
Units: participants	19			

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 Tumours 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). PFS was analyzed using K-M

methods and Greenwood's formula. Any participant who did not experience disease progression or death during the study and were censored at the last known date to be alive or without disease progression. ITT population included all screened participants (participants who signed the informed consent) who were eligible for the study.

End point type	Secondary

End point timeframe:

Up to 35 months

End point values	Atezolizumab + Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	99			
Units: months				
median (confidence interval 95%)	9.3 (7.01 to 12.40)			

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 =percentage of participants with a complete or partial response (CR/PR), on 2 consecutive investigator assessments ≥ 4 weeks apart in participants with measurable disease at baseline as determined by the investigator according to RECIST v1.1.CR =disappearance of all target lesions & any pathological lymph nodes must have a 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. Participants without a post-baseline tumor assessment were considered non-responders. 95% confidence interval (CI) was derived using Wilson score intervals. ITT population included all screened participants (participants who signed the informed consent) who were eligible for the study. Percentages have been rounded off.

End point type	Secondary

End point timeframe:

Up to 35 months

End point values	Atezolizumab + Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	99			
Units: percentage of participants				
number (confidence interval 95%)	24.2 (16.9 to 33.5)			

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. OS was analyzed using Kaplan-Meier (K-M) methods and Greenwood's formula. Any participant who did not die during the study was censored at the last known date to be alive. ITT population included all screened participants (participants who signed the informed consent) who were eligible for the study. 9999= The upper limit of the 95% CI was not estimable due to insufficient number of participants with events.

End point type	Secondary

End point timeframe:

Up to 35 months

End point values	Atezolizumab + Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	99			
Units: months				
median (confidence interval 95%)	24.8 (18.55 to 9999)			

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%, SOD must also demonstrate an absolute increase of ≥ 5 mm. TTP was analyzed using K-M methods and Greenwood's formula. Any participant who had no disease progression was censored at the last known date without disease progression. ITT population included all screened participants (participants who signed the informed consent) who were eligible for the study.

End point type	Secondary

End point timeframe:

Up to 35 months

End point values	Atezolizumab + Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	99			
Units: months				
median (confidence interval 95%)	11.2 (8.30 to 13.59)			

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=the time from the first occurrence of a documented objective response (CR/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 & any pathological lymph nodes must have a 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= 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. DOR was analyzed using K-M methods & Greenwood's formula.Any participant who did not experience disease progression or death during the study was censored at the last known date to be alive or without disease progression. ITT population.Number analyzed is the number of participants with an overall response of

End point type	Secondary

End point timeframe:

Up to 35 months

End point values	Atezolizumab + Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: months				
median (confidence interval 95%)	15.9 (7.87 to 23.74)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Started Second-line Treatment

End point title	Percentage of Participants Who Started Second-line Treatment

End point description:

Participants who started second-line of treatment were assessed. ITT population included all screened participants (participants who signed the informed consent) who were eligible for the study. Percentages have been rounded off.

End point type	Secondary

End point timeframe:

Up to 35 months

End point values	Atezolizumab + Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	99			
Units: percentage of participants				
number (not applicable)	24.2			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in International Normalized Ratio (INR)

End point title	Change From Baseline in International Normalized Ratio (INR)

End point description:

The INR is a standardized measure of the prothrombin time. Blood samples were collected from participants to evaluate coagulation parameters. Safety population included all screened participants (participants who signed the informed consent) who received at least one full or partial dose of study treatment. Number of participants analyzed is the number of participants with data available for analyses. n= number of participants with data available for analyses at the specified timepoints.

End point type	Secondary

End point timeframe:

Baseline up to Cycle 42 (1 cycle = 21 days)

End point values	Atezolizumab + Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	99			
Units: INR of prothrombin time				
arithmetic mean (standard deviation)				
Baseline (n=99) Cycle 42 (n=2)	1.1 (± 0.1) 0.1 (± 0.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Albumin-Bilirubin (ALBI) Score

End point title	Change From Baseline in Albumin-Bilirubin (ALBI) Score

End point description:

Blood samples were collected from participants to evaluate of ALBI grades. ALBI assessment grades of 1

to 3 was based on ALBI score calculation. ALBI score= log10 bilirubin (micromole per liter) [µmol/L] × 0.66 + albumin (grams per liter) [g/L] × −0.0852. ALBI score ≤ -2.60 = ALBI grade 1; -2.60 < ALBI score ≤ -1.39 = ALBI grade 2 and -1.39 < ALBI score = ALBI grade 3. Safety population included all screened participants (participants who signed the informed consent) who received at least one full or partial dose of study treatment. n= number of participants with data available for analyses at the specified timepoints.

End point type	Secondary

End point timeframe:

Baseline up to Cycle 42 (1 cycle = 21 days)

End point values	Atezolizumab + Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	100			
Units: score				
arithmetic mean (standard deviation)				
Baseline (n=100) Cycle 42 (n=2)	-2.7 (± 0.4) 0.4 (± 0.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Ascites and/or Hepatic Encephalopathy

End point title	Percentage of Participants With Ascites and/or Hepatic Encephalopathy

End point description:

Deterioration of hepatic function was monitored by presence of ascites and/or hepatic encephalopathy. Safety population included all screened participants (participants who signed the informed consent) who received at least one full or partial dose of study treatment.

End point type	Secondary

End point timeframe:

Up to approximately 32 months

End point values	Atezolizumab + Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	100			
Units: percentage of participants	17			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs and SAEs: From Cycle 1 Day 1 up to 30 days after the final dose of the study drug or until initiation of another anti-cancer therapy, whichever occurred first (up to approximately 32 months).
All cause mortality: Up to 35 months

Adverse event reporting additional description:

Safety population included all screened participants (participants who signed the informed consent) who received at least one full or partial dose of study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	Atezolizumab + Bevacizumab:

Reporting group description:

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

Serious adverse events	Atezolizumab + Bevacizumab:		
Total subjects affected by serious adverse events			
subjects affected / exposed	46 / 100 (46.00%)		
number of deaths (all causes)	51		
number of deaths resulting from adverse events	2		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour Associated Fever			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Peripheral ischaemia			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Spinal Laminectomy			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Oesophageal Variceal Ligation				
subjects affected / exposed	1 / 100 (1.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Pyrexia				
subjects affected / exposed	2 / 100 (2.00%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	2 / 100 (2.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Asthenia				
subjects affected / exposed	1 / 100 (1.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Prostatitis				
subjects affected / exposed	1 / 100 (1.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Pneumothorax				
subjects affected / exposed	1 / 100 (1.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemoptysis				
subjects affected / exposed	1 / 100 (1.00%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Chronic Obstructive Pulmonary Disease				

subjects affected / exposed	1 / 100 (1.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural Effusion				
subjects affected / exposed	2 / 100 (2.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Confusional State				
subjects affected / exposed	1 / 100 (1.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Hepatic Enzyme Increased				
subjects affected / exposed	1 / 100 (1.00%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Blood Bilirubin Increased				
subjects affected / exposed	2 / 100 (2.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Hip Fracture				
subjects affected / exposed	2 / 100 (2.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Fall				
subjects affected / exposed	1 / 100 (1.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tibia fracture				
subjects affected / exposed	1 / 100 (1.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Wound Dehiscence				
subjects affected / exposed	1 / 100 (1.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Wound evisceration				
subjects affected / exposed	1 / 100 (1.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Myocardial Infarction				
subjects affected / exposed	1 / 100 (1.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial Fibrillation				
subjects affected / exposed	1 / 100 (1.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease				
subjects affected / exposed	1 / 100 (1.00%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Hepatic Encephalopathy				
subjects affected / exposed	5 / 100 (5.00%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Spinal Cord Compression				
subjects affected / exposed	2 / 100 (2.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Encephalopathy				
subjects affected / exposed	1 / 100 (1.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Duodenal Ulcer Haemorrhage			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric Perforation			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal Perforation			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Intra-Abdominal Haemorrhage			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Oesophageal Varices Haemorrhage			
subjects affected / exposed	3 / 100 (3.00%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Abdominal Pain			
subjects affected / exposed	2 / 100 (2.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Gastrointestinal haemorrhage				
subjects affected / exposed	2 / 100 (2.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Upper Gastrointestinal Haemorrhage				
subjects affected / exposed	2 / 100 (2.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Haemoperitoneum				
subjects affected / exposed	1 / 100 (1.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemorrhoidal Haemorrhage				
subjects affected / exposed	1 / 100 (1.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal Obstruction				
subjects affected / exposed	1 / 100 (1.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ascites				
subjects affected / exposed	3 / 100 (3.00%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	1 / 100 (1.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Hepatitis				
subjects affected / exposed	2 / 100 (2.00%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	1 / 1			
Hepatic Function Abnormal				

subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Jaundice			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystitis Acute			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Tubulointerstitial Nephritis			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ureterolithiasis			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Immune-Mediated Hypothyroidism			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	3 / 100 (3.00%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cellulitis			

subjects affected / exposed	1 / 100 (1.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	2 / 100 (2.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumonia Pneumococcal				
subjects affected / exposed	2 / 100 (2.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Urinary Tract Infection				
subjects affected / exposed	2 / 100 (2.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Abdominal Sepsis				
subjects affected / exposed	1 / 100 (1.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Biliary Sepsis				
subjects affected / exposed	1 / 100 (1.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Covid-19				
subjects affected / exposed	1 / 100 (1.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Covid-19 Pneumonia				
subjects affected / exposed	1 / 100 (1.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peritonsillar Abscess				

subjects affected / exposed	1 / 100 (1.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia Aspiration				
subjects affected / exposed	1 / 100 (1.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infective exacerbation of chronic obstructive airways disease				
subjects affected / exposed	1 / 100 (1.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory Tract Infection				
subjects affected / exposed	1 / 100 (1.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spontaneous Bacterial Peritonitis				
subjects affected / exposed	1 / 100 (1.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Subdiaphragmatic Abscess				
subjects affected / exposed	1 / 100 (1.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Dehydration				
subjects affected / exposed	1 / 100 (1.00%)			
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	98 / 100 (98.00%)		
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	42 / 100 (42.00%) 56		
General disorders and administration site conditions Mucosal Inflammation subjects affected / exposed occurrences (all)	9 / 100 (9.00%) 14		
Pain subjects affected / exposed occurrences (all)	7 / 100 (7.00%) 8		
Pyrexia subjects affected / exposed occurrences (all)	13 / 100 (13.00%) 16		
Asthenia subjects affected / exposed occurrences (all)	46 / 100 (46.00%) 78		
Oedema subjects affected / exposed occurrences (all)	5 / 100 (5.00%) 5		
Fatigue subjects affected / exposed occurrences (all)	5 / 100 (5.00%) 6		
Oedema Peripheral subjects affected / exposed occurrences (all)	11 / 100 (11.00%) 16		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	11 / 100 (11.00%) 11		
Epistaxis subjects affected / exposed occurrences (all)	7 / 100 (7.00%) 7		

Catarrh subjects affected / exposed occurrences (all) Productive Cough subjects affected / exposed occurrences (all) Dysphonia subjects affected / exposed occurrences (all)	 5 / 100 (5.00%) 5 5 / 100 (5.00%) 5 9 / 100 (9.00%) 10		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	 10 / 100 (10.00%) 11		
Investigations Alanine Aminotransferase Increased subjects affected / exposed occurrences (all) Weight Decreased subjects affected / exposed occurrences (all) Amylase Increased subjects affected / exposed occurrences (all) Platelet Count Decreased subjects affected / exposed occurrences (all) Lipase Increased subjects affected / exposed occurrences (all) Blood Bilirubin Increased subjects affected / exposed occurrences (all)	 5 / 100 (5.00%) 7 6 / 100 (6.00%) 6 6 / 100 (6.00%) 8 9 / 100 (9.00%) 9 9 / 100 (9.00%) 14 9 / 100 (9.00%) 10		
Nervous system disorders Headache subjects affected / exposed occurrences (all) Dysgeusia	 13 / 100 (13.00%) 15 		

subjects affected / exposed	5 / 100 (5.00%)		
occurrences (all)	5		
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	11 / 100 (11.00%)		
occurrences (all)	18		
Anaemia			
subjects affected / exposed	6 / 100 (6.00%)		
occurrences (all)	8		
Gastrointestinal disorders			
Haemorrhoids			
subjects affected / exposed	5 / 100 (5.00%)		
occurrences (all)	5		
Dyspepsia			
subjects affected / exposed	6 / 100 (6.00%)		
occurrences (all)	7		
Dry Mouth			
subjects affected / exposed	6 / 100 (6.00%)		
occurrences (all)	8		
Ascites			
subjects affected / exposed	9 / 100 (9.00%)		
occurrences (all)	11		
Nausea			
subjects affected / exposed	11 / 100 (11.00%)		
occurrences (all)	17		
Abdominal Pain Upper			
subjects affected / exposed	11 / 100 (11.00%)		
occurrences (all)	13		
Vomiting			
subjects affected / exposed	13 / 100 (13.00%)		
occurrences (all)	15		
Constipation			
subjects affected / exposed	20 / 100 (20.00%)		
occurrences (all)	22		
Abdominal Pain			

subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all)	22 / 100 (22.00%) 32 30 / 100 (30.00%) 64		
Hepatobiliary disorders Hyperbilirubinaemia subjects affected / exposed occurrences (all) Hypertransaminasaemia subjects affected / exposed occurrences (all)	 10 / 100 (10.00%) 13 8 / 100 (8.00%) 10		
Skin and subcutaneous tissue disorders Skin Lesion subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all)	 5 / 100 (5.00%) 5 5 / 100 (5.00%) 7 24 / 100 (24.00%) 29		
Renal and urinary disorders Proteinuria subjects affected / exposed occurrences (all)	 18 / 100 (18.00%) 23		
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	 14 / 100 (14.00%) 14		
Musculoskeletal and connective tissue disorders Pain In Extremity subjects affected / exposed occurrences (all) Arthralgia	 7 / 100 (7.00%) 8 		

subjects affected / exposed	17 / 100 (17.00%)		
occurrences (all)	19		
Myalgia			
subjects affected / exposed	7 / 100 (7.00%)		
occurrences (all)	8		
Back Pain			
subjects affected / exposed	14 / 100 (14.00%)		
occurrences (all)	17		
Infections and infestations			
Respiratory Tract Infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	7 / 100 (7.00%)		
occurrences (all)	8		
Nasopharyngitis			
subjects affected / exposed	12 / 100 (12.00%)		
occurrences (all)	13		
Covid-19			
subjects affected / exposed	21 / 100 (21.00%)		
occurrences (all)	22		
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	22 / 100 (22.00%)		
occurrences (all)	31		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 March 2023	1.Immunosuppressive medications were removed from the prohibited therapy and added to the cautionary therapy to align with atezolizumab management guidelines in Appendix 10 that permit use of immunosuppressive medications for the treatment of corticosteroid-refractory immune-mediated adverse events. 2. The list of identified risks for atezolizumab was revised to include pericardial disorders, myelitis, and facial paresis. 3. Hemophagocytic lymphohistiocytosis was updated from a potential risk to an identified risk associated with atezolizumab and language has been revised accordingly. 4. The list of adverse events of special interest has been revised to include myelitis and facial paresis. 5. Appendix 7 was revised to indicate that caution should be used when considering atezolizumab for patients who have previously experienced a severe or life-threatening skin adverse reaction or pericardial disorder while receiving another immunostimulatory anticancer agent. 6. Risks and management guidelines for atezolizumab were updated to align with the Atezolizumab Investigator's Brochure Version 19.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported